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TITLE: Tuberous Sclerosis Complex National Database

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CONTRACTING ORGANIZATION: The University of Texas Southwestern Medical Center
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14. **ABSTRACT**

A Consortium was formed in July 2002 by the Tuberous Sclerosis Alliance (TSA) and tuberous sclerosis (TS) clinic personnel nationwide to begin discussions of natural history studies and development of a comprehensive clinical database (DB) to be used for both research and clinical purposes. The Consortium proposes to characterize the natural history of tuberous sclerosis complex (TSC) through development of an internet-based DB to collect comprehensive data on individuals with TSC. To date, we have established Working Groups (WG) to define the specific aims for the natural history study; established an Advisory Panel (AP) to serve in an advisory capacity to the Consortium; established a Steering Committee (SC) to oversee development of the DB, and assist in drafting a Consortium Agreement by which members of the TSCCDC will adhere; held meetings to discuss development of data collection tools and drafted a data collection tool. In July of 2005, TSA assumed control of the development process and contracted with a computer software designer to begin development of the DB.

15. SUBJECT TERMS
Tuberous Sclerosis Complex, Database, Natural History

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Introduction

Our work involves the creation of an internet-based database (DB) to collect comprehensive data on individuals with tuberous sclerosis complex (TSC) in order to better define the natural history of TSC and to enable clinical research in TSC. This DB will be developed through the collaborative efforts of clinicians and scientists from all major TSC clinics in the United States and the Tuberous Sclerosis Alliance (TSA). The scope of this award allowed us to establish the administrative framework for the development of the DB and to commence the initial stages of DB development. DB development is ongoing and is now being overseen by the TSA. Once the DB is fully developed, subjects will be recruited on a voluntary basis from multiple tuberous sclerosis clinics throughout the United States, possibly from select international sites, as well as the TSA. Data is to be collected both retrospectively and prospectively, with intent to capture data longitudinally.

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Body

The Tuberous Sclerosis Complex Clinical Database Consortium (TSCCDC or Consortium) was formed in July 2002 to begin discussions of a natural history study approach to understanding Tuberous Sclerosis Complex (TSC) and the development of a comprehensive clinical database (DB) that could be used for both research and clinical purposes. The TSCCDC is composed of members of the major TSC clinics in the United States (US), one TSC clinic in the United Kingdom (UK), and the Tuberous Sclerosis Alliance (TSA).

A significant objective of the TSCCDC is to define the natural history and variability of TSC over the lifespan of individuals with the disease. Improved characterization of all clinical aspects of TSC will allow for more accurate prognosis of disease course, assist in the identification and development of targeted treatments, and will enhance our ability to gauge response to treatments as they are developed. Information from this study will also provide important insights about biological mechanisms of epilepsy, cognitive development, behavioral disorders, and cancer as these problems relate to individuals with TSC, as well as to the general population.

A mechanism by which the above-mentioned objective will be achieved is through the development of an internet-based DB used to collect comprehensive clinical information on individuals with TSC. The DB is being developed through the collaborative efforts of clinicians and scientists who make up the TSCCDC.

Through natural history studies and the establishment of the DB, the TSCCDC will provide for the acquisition, storage, and utilization of clinical data on approximately 2,000 individuals with TSC. This information will allow for a better description of the clinical course of individuals throughout the life cycle. The DB will also serve as an important research tool in launching investigations on specific clinical problems and TSC treatments. While several institutions have developed DBs to manage their TSC clinical data, there are no DBs of the breadth, magnitude and power as the one we have proposed. The TSCCDC chose to initiate development of the DB at The Scottish Rite Hospital for Children (TSRHC) because of prior experience in the development of a similar DB for another complex neurological disorder, holoprosencephaly (HPE).

As required by regulations set forth by the Department of Defense (DOD) Congressionally Directed Medical Research Programs (CDMRP) prior to formal application of our grant proposal, several tasks were outlined. One such task was the creation of a Statement of Work (SOW).

The SOW was submitted in May 2004 to the CDMRP as directed by the grant submission requirements. Once the grant SOW was approved, work began in earnest on the accomplishment of the tasks delineated within the SOW. The SOW has been provided in **Appendix B**.

One of the first tasks was to establish an administrative structure to guide development of the DB. Three key areas either identified by the TSCCDC or required by the DOD as part of this

structure include a Steering Committee (SC), an Advisory Panel (AP), and Working Groups (WG).

WGs were originally established in November 2003 as a result of the work of the TSCCDC. These groups were comprised of professionals in the healthcare field and were created to reflect the key areas of interest in the treatment and research of subjects with TSC. These areas include epilepsy, cardiology, renal/urology, pulmonology, dermatology, cognition and behavior, genetics, and other organ involvement. The WG members were given the task of 1) identifying research questions regarding the natural history and progression of TSC and 2) identifying key fields to be included in the data collection tools. Since their inception, the WGs have met via teleconferencing on several occasions and in person in April 2004 and November 2004. A complete list of WG members is included in **Appendix C**.

In April 2004, a meeting was held at TSRHC in Dallas, Texas (TX), to further the progress of the DOD Natural History Development Award proposal. Those in attendance established an SC and an Executive Steering Committee (ESC) as required by DOD regulations. Members include both clinicians and consumers. Names and affiliations for both the SC and ESC have been provided in **Appendix D**. The function of the SC was to direct the development of the DB and data collection tools. The ESC was created in order to make decisions that needed to be made quickly and to approve the direction of project development.

Planning for the establishment of an AP, as set forth in the guidelines for the Natural History Planning Award, was begun at this meeting as well. Key advisory disciplines were identified and potential member names were suggested by the newly formed SC. Other members of the TSCCDC not on the SC were asked to submit possible AP members. A complete list of AP members is included in **Appendix E**. The AP includes both clinicians and consumers as required by the DOD. The potential members were contacted over the course of the next few months with most members in place by early fall 2004. The final members were secured in January 2005. The AP was in place to serve as a sounding board for the WG and SC members as they worked on field development and data collection tools. The AP members agreed to be available for one-two meetings per year but were primarily available by phone or email.

An application was made to the DOD by Dr. Steven P. Sparagana on behalf of the TSCCDC for a Natural History Planning Award in May 2004. The planning grant was officially awarded in September 2004. Work continued on the creation of the proposed DB in the meantime.

A meeting was held in November 2004, at TSRHC to continue work on establishing data fields for a TSC DB. Members of the SC, some members of the WGs, and Information Technology (IT) from TSRHC met to discuss key data points that would be collected in the DB. Several areas were discussed in detail and initial fields were established. It was decided that a data collection tool would be created and circulated to several of the participating sites for a trial use period.

At the November 2004 meeting, it was decided that Dr. John Bissler from Cincinnati Children's Hospital Medical Center would submit a Natural History Study grant proposal on the renal

aspects of TSC on behalf of the TSCCDC. The proposal entitled Tuberous Sclerosis Complex Natural History Study: Renal Manifestations, was submitted in the Spring 2005.

Upon completion of the November 2004 meeting, the proposed fields were circulated to the WG and SC members for review. Based upon the results of the November meeting and feedback from the SC members, work was begun on an initial data collection tool.

Over the course of the next few months, drafts of specific sections of the tool were circulated to corresponding WG members as each section was completed. Once input was received from the WG members, revisions were considered and made if deemed appropriate. The tool was to be distributed to the entire WG membership upon completion.

The WGs have almost completed their work at this point. The WG members are available for further consultation if needed and will be given the opportunity to review the data collection tools prior to use. To date, their work has resulted in the development of drafts of an Initial Data Collection Tool and a Mortality Report Tool. These drafts are provided in **Appendices F and G**. There is work remaining to be done on a Follow-up Visit Data Collection Tool and a Quality of Life Data Collection Tool. Work remains to be done on the Cognitive and Development section of the Initial Data Collection Tool. A TSC patient registry has also been discussed but has not been developed yet.

Prior to widespread use, the data collection tools will undergo a trial. These tools will have undergone review by the Institutional Review Board (IRB) associated with each institution or a central IRB. Once the trail of the data collection tools is complete, any recommended modifications will be made. The final tools will then undergo re-review by the IRB. At that time consent forms will have been developed and submitted for approval as well. Only after all the trials and approval processes are complete will any subject enrollment begin. DB development will continue during the trial period.

As part of the initial proposal process, specific aims of a future Natural History Study were developed and were included in the original grant proposal. During the meeting in November 2004, these specific aims were expanded upon. Several potential research questions/hypotheses were identified as well. Specific aims and representative research questions have been provided in **Appendix H**.

On April 9, 2005, Drs. Steven Sparagana and E. Steve Roach presented a brief review entitled Clinical Features and Natural History of TSC at the TSC/LAM (Lymphangioleiomyomatosis) International Research Symposium in Cincinnati, Ohio (OH). This review included a project update on the status of DB development. A copy of the abstract has been included as **Appendix I**.

Several administrative changes occurred at TSA during the course of the award cycle, some of which have directly affected the direction of DB development. The most notable change is that Nancy Taylor was hired as the new president of TSA in September 2004. Ms. Taylor has enthusiastically embraced the DB and Natural History study and has been instrumental in expediting transfer of the DB to the TSA ahead of schedule.

Other administrative changed of note include the hiring of Jo Anne Nakagawa to facilitate the project internally within the TSA. Michael Cinkosky of Tesuji, Inc. was contracted to develop the software for the DB. CVs for both Ms. Nakagawa and Mr. Cinkosky are attached as **Appendices J and K**.

In July 2005, representatives from TSA, TSRHC and Tesuji, Inc., a software development company, met in Dallas, TX, to discuss ongoing development of the DB. It was decided that TSA would assume responsibility to develop and maintain the DB from that time forward. Nancy Taylor communicated this to the members of the TSCCDC, SC, AP and WGs in a letter dated September 21, 2005. This letter has been attached as **Appendix L**. The Tesuji, Inc., development plan for the DB has been attached as **Appendix M**.

The TSA staff is presently developing a strategic plan on how the project will proceed. As a result of the shift in DB development site and in the above-mentioned changes in management, there will likely be modifications to the administrative structure outlined previously. However, the specific aim and overall goals of the project remain unchanged.

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Key Research Accomplishments

- Solidified the relationship of the TSC clinicians and researchers who form the Tuberous Sclerosis Complex Clinical Database Consortium (TSCCDC). This group has worked together to ensure the development of a multicenter TSC DB.
- Established the administrative structure from the members of the TSCCDC. This administrative structure will oversee the continued development of the DB and aid in the identification of Natural History Studies that will ultimately utilize this DB.
- Formulated specific aims and hypotheses which may be further addressed in future Natural History Studies.
- Development of data collection tools including an Initial Data Collection Tool and a Mortality Report Tool.
- Based on the initial progress of the DB and success of the TSCCDC collaboration, Dr. John Bissler from Cincinnati Children's Hospital Medical Center submitted a Natural History Study grant proposal on the renal aspects of TSC on behalf of the TSCCDC. The proposal entitled Tuberous Sclerosis Complex Natural History Study: Renal Manifestations, was submitted in the Spring 2005 and awarded to Dr. Bissler in September 2005.

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Reportable Outcomes

- Data Collection Tools

The work on the project for this Natural History Development Award has generated two very important data collection tools in draft form. These are the Initial Data Collection Tool and the Mortality Report Tool. These tools have been provided in this document as Appendices F and G, respectively.

The focus of this project was to develop a DB that would be used by TSC clinicians and researchers in future Natural History Studies. Before any DB could be built or any data collected, it was crucial to create data collection tools that would be used to collect the information needed to further our knowledge of TSC. These tools would then be used to help guide the computer software developer in creating a usable, complete DB.

As mentioned in the Body of this document, many groups have been involved in the creation of these documents and will continue to be involved as the project progresses. These groups will be involved in development of future data collection tools as well.

- Funding for Natural History Study Award

Based on the initial progress of the DB, Dr. John Bissler from Cincinnati Children's Hospital Medical Center submitted a Natural History Study grant proposal on the renal aspects of TSC on behalf of the Tuberous Sclerosis Complex Clinical Database Consortium (TSCCDC). The proposal entitled Tuberous Sclerosis Complex Natural History Study: Renal Manifestations, was submitted in the Spring 2005. The grant was awarded to Dr. Bissler in September 2005.

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Conclusions

For many years, key Tuberous Sclerosis Complex (TSC) clinicians and researchers have expressed the desire for a multicenter TSC Database (DB) that would allow for the collection of comprehensive data on individuals with TSC. The Tuberous Sclerosis Complex Clinical Database Consortium was formed with the intent to create such a DB.

This Natural History Planning Award has fostered a renewed desire to achieve the goal of a multicenter DB. It has allowed the TSCCDC to develop into a more cohesive group whose goal is the creation of a DB that will facilitate Natural History Studies leading to a better understanding of TSC.

The basic administrative framework was established as well as the commencement of the initial stages of DB development. Data collection tools, which are key to the development of a DB that is both comprehensive and easy to use, have been developed. It is our hope that these tools will used on a trial basis in the near future.

The Tuberous Sclerosis Alliance (TSA) has assumed a more active role in the development of the DB by hiring a DB manager to oversee the development effort and contracting with a software developer. We expect to see continued progress over the remainder of the funding cycle and beyond.

References

There were no relevant references used in the preparation of this annual report.

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Appendix A – Abbreviations

AP	Advisory Panel
CCB	Change Control Board
CDMRP	Congressionally Directed Medical Research Programs
CV	Curriculum Vitae; Curricula Vitae
DB	Database
DOD	Department of Defense
ESC	Executive Steering Committee
HPE	Holoprosencephaly
IRB	Institutional Review Board
IT	Information Technology
LAM	Lymphangioleiomyomatosis
OH	Ohio
SC	Steering Committee
SOW	Statement of Work
TSA	Tuberous Sclerosis Alliance
TSC	Tuberous Sclerosis Complex
TSCCDC	Tuberous Sclerosis Complex Clinical Database Consortium
TSRHC	Texas Scottish Rite Hospital for Children
TX	Texas
US	United States
UK	United Kingdom
WG	Working Group(s)

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Appendix B – Statement of Work

Task 1: Set up administrative structure to oversee development of the database (DB)

- Working groups (WG) established November 2003. Several groups have been meeting regularly via teleconferences and will continue to do so.
    - Task was to develop fields to be included in DB by establishing key scientific questions. Focus areas include: Epilepsy/EEG, Brain Lesions/MRI/other CNS Imaging, Dermatology, Renal, Neuropsychological/Behavioral/Cognition, Pulmonary, Genetics/Family History, Other Organ Systems and Registry (WG pending).
    - A list of WG members will be provided upon request.
- Planning meeting held on April 13, 2004.
- Steering Committee (SC) formally established April 13, 2004.
    - Members are listed in Proposal Body.
- Formation of Advisory Panel. April-August 2004.
    - Names were submitted for review by members of the SC. Contact will be made and members secured by end of August 2004.
- Identification of Phase I and Phase II sites. April-May 2004.
    - Phase I sites will be the primary sites involved in development and testing of the DB and for subject enrollment; Phase II sites will be added once the DB is up and running smoothly.
    - Sites are listed in Proposal Body.

Task 2: Drafting and approval of Consortium Agreement

- Consortium Agreement drafted January 2004.
    - Draft copy is included with the Proposal under the Administrative Documentation section.
- Final draft to be circulated between SC, Phase I and Phase II site members. July 2004.
- Approval and signatures to be obtained by the end of July 2004.

Task 3: Development of data fields for DB

- Fields for DB to be developed by WGs. January-December 2004.
- WG will also define how to standardize data between clinical sites, e.g., volumetric measurement of cortical tubers on MRI. January-December 2004.
- Teleconferences will be held throughout 2004 to accomplish this task.

Task 4: Meeting of key WG members with Texas Scottish Rite Hospital for Children (TSRHC) Information Technology (IT) staff

- Key WG members, SC members, Advisory Panel and IT staff to finalize data fields. October-November 2004.
- Revised data fields to be circulated to all WG members for final approval. November-December 2004.
- Data fields presented to IT staff to commence DB construction. December 2004.

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Task 5: Creation of the DB

- Identification of a third-party vendor for programming needs. November-December 2004.
- Initial programming of fields. January-September 2005.

Task 6: Initial DB prototype review and revision

- Meeting with key WG members, SC, and IT staff to review initial prototype. Spring 2005.
- Revision of DB. September-December 2005.

Task 7: Institutional Review Board approval

- Will seek overall project approval August 2004.
- Consent forms to be written and submitted for approval. December 2005-April 2006.

Task 8: Define patient selection process

- Identification of sample size and description of patient population at each site. July-August 2004.
- Identify methods to minimize selection bias (e.g., to ensure that mildly affected individuals are proportionally represented in DB). July-August 2004.

Task 9: DOD TSC Natural History Study grant proposal

- Prepare and submit DOD TSC Natural History Study grant proposal March-May 2005.

Task 10: Formation of a patient-initiated registry

- Registry to be developed as a separate component of the DB to collect contact and demographic information from potential subjects for future TSC research projects. June-August 2005.

Task 11: Development of data collection tools

- Develop data collection forms. December 2005-June 2006.
- Meeting with key WG members and SC members to finalize data collection tools. Spring 2006.
- Develop training protocol. December 2005-June 2006.

Task 12: Site visit for training

- Site visits to Phase I clinics for training of data collection personnel January-March 2006.
    - This task may be accomplished by data collection personnel visiting TSRHC for training.

Task 13: Application for Certificate of Confidentiality

- Application will be made to the Department of Health and Human Services for the DB project as a whole. May 2006.

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Task 14: Development of information dissemination web site

- Develop a web site that provides information about the TSC National DB and gives some statistics about enrollment, projects to date, planned projects, recruitment information and a link to the TSC patient-initiated registry. July-August 2006.

Task 15: Piloting test DB

- Troubleshooting data input/output. January 2006.
- Revision of DB. February 2006.
- Subsequent DB trial. March 2006.

Task 16: Development of patient recruitment tools

- Patient recruitment tools to be developed by key Steering Committee and Phase I site members. January 2006-July2006.
    - Tools to include brochures, videos, and other materials as yet to be determined.
- All tools will be submitted for IRB approval prior to use.

Task 17: Database go-live

- Subject recruitment and data entry to begin. July 2006.

Appendix C – Working Groups

1. CNS

1A - Epilepsy/EEG

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**Aimee Williams is no longer affiliated with UTH and lives outside of the US. She is no longer available for this Working Group.

Tuberous Sclerosis Complex (TSC) Natural Database (DB)
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PI: Dr. Steven Sparagana

Appendix D – Executive Steering Committee and Steering Committee

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**Cheryl Dunigan is no longer working with the TSA and is not available for this committee.

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Appendix E – Advisory Panel

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Appendix F – Data Collection Tool

Tuberous Sclerosis Complex (TSC) Database
Data Collection Form -- Initial Visit

(Please print all information and check appropriate responses)

Today's Date (mm/dd/yyyy) ___ / ___ / _____

I. DEMOGRAPHICS

Subject's Full Name (first/middle/last): _____

Age: ____ Date of Birth (mm/dd/yyyy):___/___/____ Birthplace (City/State/Country): _____ Sex: ❑M ❑F

Race (check all that apply): ❑W-White ❑H-Hispanic ❑B-Black ❑OA-Oriental Asian ❑AI-American Indian ❑PI-Pacific Islander ❑MEA-Middle Eastern Asian ❑Other (list): _____

Highest school grade level attended: ❑ elementary ❑ junior high ❑ high school ❑ junior college ❑ college ❑ post graduate

Primary Language Spoken in the Household: _____ Occupation (If applicable): _____

Age TSC first diagnosed: ____month(s) ____year(s) Diagnosis classified as: ❑ Definite ❑ Probable ❑ Possible

Biological Mother's Name (first/middle/maiden/last): _____

Age:____ Date of Birth (m/d/y):___/___/___ Race (check all that apply): ❑W ❑H ❑B ❑OA ❑AI ❑PI ❑MEA ❑Other _____

Occupation: _____

Highest school grade level attended: ❑ elementary ❑ junior high ❑ high school ❑ junior college ❑ college ❑ post graduate

Street Address: _____ Apartment #: _____

City, State: _____ Zip Code: _____ Country: _____

Home Phone #: _____ Work #: _____ Alternate #: _____

Fax #:_____ E-mail Address: _____

Biological Father's Name (first/middle/last): _____

Age:____ Date of Birth (m/d/y):___/___/___ Race (check all that apply): ❑W ❑H ❑B ❑OA ❑AI ❑PI ❑MEA ❑Other _____

Occupation: _____

Highest school grade level attended: ❑ elementary ❑ junior high ❑ high school ❑ junior college ❑ college ❑ post graduate

Street Address: _____ Apartment #: _____

City, State: _____ Zip Code: _____ Country: _____

Home Phone #: _____ Work #: _____ Alternate #: _____

Fax #:_____ E-mail Address: _____

Name of Legal Guardian (first/middle/last): _____ Relationship to patient:_____

Street Address:_____ Apartment #: _____

City, State: _____ Zip Code: _____ Country: _____

Home Phone #: _____ Work #: _____ Alternate #: _____

Fax #:_____ E-mail Address: _____

For Center Use Only

Database ID:	**TSC Consortium Site:**	**Medical Record #:**
DB Consent: ❑ Y ❑ N	Form completed by:	Registry: ❑ Y ❑ N

Subject name: First, Middle, Last _____ **DOB:**_____

II. VITAL PHYSICAL DATA

Height _____ cm	Pulse _____
Weight _____ kg	Respirations _____
FOC _____ cm	BP _____

III. GENETICS

GENETIC TESTING

Was prenatal TSC genetic testing performed: ❑ Yes ❑ No ❑ Unknown
If yes, what was the result: ❑ TSC1 ❑ TSC2 ❑ Unknown

Was TSC genetic testing performed: ❑ Yes ❑ No ❑ Unknown
If yes: ❑ Athena or Research lab: ❑ Northrup ❑ Kwiatkowski ❑ Sampson ❑ Netherlands ❑ Other (list)
_____

Was mutation identified: ❑ Yes ❑ No ❑ Unknown
If yes: ❑ TSC1 ❑ TSC2 Mutation (list) _____

Type of mutation (check all that apply):
Large gene deletions/rearrangements/insertions ❑Yes ❑No ❑Unknown
Small mutation ❑Yes ❑No ❑Unknown
If yes, check the mutation that applies: ❑Protein truncation ❑Small deletion/insertion ❑Nonsense ❑Missense ❑Unknown
Other variation (polymorphism) detected in ❑TSC1 ❑TSC2

If mutation was not found, are you enrolled in another genetic study: ❑Yes ❑No ❑Unknown
If yes, check all that apply: ❑Northrup ❑Sampson ❑Other (list) _____

Was blood or tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA)
❑Yes ❑No ❑Unknown
If yes, indicate location of bank and physician who banked sample: _____
_____

FAMILY HISTORY OF TSC

Is subject the result of a multiple gestation: ❑Yes ❑No ❑Unknown (e.g., adopted, foster child, etc.)

If subject is the product of a multiple birth, how many siblings: _____
Do any have TSC: ❑Yes ❑No ❑Unknown
Are siblings: ❑Fraternal ❑Identical ❑Mixed fraternal and identical

If subject is a twin, which type: ❑Fraternal ❑Identical
Does twin have TSC: ❑Yes ❑No ❑Unknown

Are there other multiple births in family history: ❑Yes ❑No ❑Unknown

Familial history of TSC: ❑Yes ❑No ❑Unknown ❑Adopted
If yes, how many generations are affected: ❑1 ❑2 ❑3 ❑4 ❑5 ❑>5 ❑Unknown
How many known affected family members: ❑1 ❑2 ❑3 ❑4 >❑4 ❑Unknown
If yes: ❑Mosaic ❑within one generation ❑Mosaic parent/germline child(ren) – two generations ❑Multigenerational

Have subject's parents had any of the following exams/evaluations:
Mother: ❑Yes ❑No ❑Unknown
If yes, indicate which tests were performed:
❑TSC genetic testing
❑Brain imaging

❑Renal imaging
❑Eye exam
If eye exam was performed, check all that apply: ❑Ophthalmologist ❑Optometrist ❑ Other MD
❑Skin exam
If skin exam was performed, check all that apply: ❑Dermatologist ❑Other MD

Father: ❑Yes ❑No ❑Unknown
If yes, indicate which tests were performed:
❑TSC genetic testing
❑Brain imaging
❑Renal imaging
❑Eye exam
If eye exam was performed, check all that apply: ❑Ophthalmologist ❑Optometrist ❑ Other MD
❑Skin exam
If skin exam was performed, check all that apply: ❑Dermatologist ❑Other MD

ASSISTED REPRODUCTIVE TECHNOLOGY

Was subject conceived using Assisted Reproductive Technology (ART)	❑Yes	❑No	❑Unknown
Egg donation	❑Yes	❑No	❑Unknown
Sperm donation	❑Yes	❑No	❑Unknown
In Vitro Fertilization (IVF)	❑Yes	❑No	❑Unknown
IVF + Intracytoplasmic sperm injection (ICSI)	❑Yes	❑No	❑Unknown
Preimplantation Genetic Diagnosis (PGD)	❑Yes	❑No	❑Unknown
Singleton birth	❑Yes	❑No	❑Unknown
Multiple birth	❑Yes	❑No	❑Unknown

If multiple, how many: _____

IV. PRENATAL HISTORY

Was subject's diagnosis of TSC discovered during gestation: ❑Yes ❑No ❑Unknown
If yes, by which method:
❑Chorionic villus sampling (CVS)/genetic testing
❑Amniocentesis/genetic testing
❑High-resolution echocardiography
❑Routine ultrasound
❑Fetal MRI
❑Other (list) _____

Were there any complications during subject's gestation: ❑Yes ❑No ❑Unknown
If yes, indicate which complications occurred:
❑Maternal gestational diabetes
❑Maternal infection
❑Maternal seizures
❑Maternal substance abuse
❑Premature rupture of membranes
❑Premature birth
❑Other (list) _____
_____

Were any of the following procedures performed during subject's gestation: ❑Yes ❑No ❑Unknown
If yes, check all that apply:
❑Chorionic villus sampling (CVS)
❑Amniocentesis
❑Genetic testing
❑Routine ultrasound

❑Fetal MRI
❑Other (list) _____
_____

What was the estimated gestational age (EGA) at birth: _____ weeks

Was subject born by: ❑Vaginal delivery ❑Cesarean section ❑Unknown

Were there any complications during or immediately after birth: ❑Yes ❑No ❑Unknown
If yes, check all that apply:
❑Prolonged labor
❑Failure to progress
❑Decreased fetal heart rate
❑Meconium present
❑Low Apgar scores
1-minute score _____ ❑Unknown
5-minute score _____ ❑Unknown
❑Resuscitation:
❑Major ❑Minor
❑Seizure
❑Other (list) _____
_____

V. DERMATOLOGY

Has subject ever been evaluated by dermatologist for TSC finding: ❑Yes ❑No ❑Unknown
If yes, ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by dermatologist: ❑Yes ❑No ❑Unknown

SKIN

Hypomelanotic macules: ❑Yes ❑No ❑Unknown
If yes: ❑1-3 ❑4-6 ❑≥6
Size and location of largest three:
Size _____ cm; location _____
Size _____ cm; location _____
Size _____ cm; location _____
Diagnosed by: ❑Visual inspection ❑Woods lamp
Subject's age when hypomelanotic macules first noted: _____ month(s) _____ year(s)
Treatment: ❑Yes ❑No ❑Unknown
If yes: ❑Makeup ❑Other (list) _____

Confetti lesions: ❑Yes ❑No ❑Unknown
If yes: ❑Right arm (RA) ❑Right leg (RL) ❑Left arm (LA) ❑Left leg (LL) ❑Other (list) _____
Subject's age when confetti lesions first noted: _____ month(s) _____ year(s)

Scalp fibroma: ❑Yes ❑No ❑Unknown
Signs and symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Difficulty combing/brushing hair
❑Pain
❑Bleeding
❑Infection
❑Other (list) _____
Treatment: ❑Yes ❑No ❑Unknown
❑Surgical excision
❑Other (list) _____
Subject's age when scalp fibroma first noted: _____ month(s) _____ year(s)

Forehead fibroma: ❑Yes ❑No ❑Unknown
Signs and symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Bleeding
❑Other (list) _____
Treatment: ❑Yes ❑No ❑Unknown
❑Surgical excision
❑Other (list) _____
Subject's age when forehead fibroma first noted: _____ month(s) _____ year(s)

Angiofibroma: ❑Yes ❑No ❑Unknown
If yes: ❑<10 ❑≥10
Texture: ❑Flat ❑Raised
Location: ❑Cheeks ❑Chin ❑Nose ❑Nasolabial folds ❑Forehead
Distribution: ❑Unilateral ❑Bilateral
Color (does not apply to black skin): ❑Normal ❑Pink ❑Red ❑Brown
Signs and symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Bleeding
❑Infection
Other (list) _____
Treatment: ❑Yes ❑No ❑Unknown
If yes, what treatment was performed (choose all that apply):

Treatment	Number of times treatment was performed
❑Laser removal	_____
❑Dermabrasion	_____
❑Cryosurgery	_____
❑Surgical excision	_____
❑Other (list) _____	_____

Subject's age when angiofibroma first noted: _____ month(s) _____ year(s)

Shagreen patch: ❑Yes ❑No ❑Unknown
If yes, location: ❑Lumbosacral Region ❑Other (list) _____
Treatment: ❑Yes ❑No ❑Unknown
If yes, what treatment was performed (choose all that apply):
❑Surgical excision
❑Other (list) _____
Subject's age when shagreen patch first noted: _____ month(s) _____ year(s)

Other: (choose all that apply)
❑Café au lait macule
❑Skin tags
❑Miliary fibroma (defined as slightly raised skin papules tinier than a pin head)
❑Other (list) _____

Biopsy:
Was a biopsy performed on any of the above mentioned skin findings: ❑Yes ❑No ❑Unknown
If yes, indicate tissue/finding: _____
Results if known: _____

NAILS

Ungual fibroma: ❑Yes ❑No ❑Unknown
If yes, location (indicate digit(s) - 1, 2, 3, 4, 5 with thumb and great toe being digit #1):
❑Right hand (RH) _____
❑Left hand (LH) _____

❑Right foot (RF) _____
❑Left foot (LF) _____
Symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):

Indicate all digits affected (e.g., RH-1, LF-2)

❑Bleeding _____
❑Infection _____
❑Loss of nail _____
❑Other (list):_____ _____

Treatment: ❑Yes ❑No ❑Unknown
❑Surgical excision Number of times treatment performed _____
If excised, did any of excised tissue recur: ❑Yes ❑No ❑Unknown
If yes, which tissue recurred: _____
❑Other (list) Number of times treatment performed _____

HAIR

Poliosis: ❑Yes ❑No ❑Unknown
If yes, indicate location: ❑Scalp hair ❑Eyebrows ❑Eyelashes ❑Other (list) _____

VI. DENTAL

Has subject ever been evaluated by dentist for TSC finding: ❑Yes ❑No ❑Unknown
If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by dentist: ❑Yes ❑No ❑Unknown

Pitting: ❑Yes ❑No ❑Unknown
If yes, is/was pitting present in baby teeth: ❑Yes ❑No ❑Unknown ❑N/A
If yes, number of pits: ❑1-5 ❑6-10 ❑11-15 ❑>15
Are any pits crater-like: ❑Yes ❑No ❑Unknown
Is pitting present in permanent teeth: ❑Yes ❑No ❑Unknown ❑N/A
If yes, number of pits: ❑1-5 ❑6-10 ❑11-15 ❑>15
Are any pits crater-like: ❑Yes ❑No ❑Unknown
Symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Pain
❑Secondary decay
❑Other (list) _____
Treatment: ❑Yes ❑No ❑Unknown
If yes, list treatment: _____

Gingival Fibroma: ❑Yes ❑No ❑Unknown
If yes, number present: ❑1 ❑2-4 ❑>4
Symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Bleeding
❑Pain
❑Other (list) _____
Treatment: ❑Yes ❑No ❑Unknown
If yes, indicate what treatment was performed:
❑Surgical excision Number of times treatment performed _____
If excised, did any of excised tissue recur: ❑Yes ❑No ❑Unknown
❑Other (list) _____

Gingival Hyperplasia: ❑Yes ❑No ❑Unknown
If yes, has subject been prescribed phenytoin (PHT): ❑Yes ❑No ❑Unknown
If PHT was prescribed, ❑drug used in past ❑drug currently used
Symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Bleeding
❑Other (list) _____
Treatment: ❑Yes ❑No ❑Unknown
If yes, indicate what treatment was performed:
❑Surgical excision Number of times treatment performed _____
If excised, did any of excised tissue recur: ❑Yes ❑No ❑Unknown
❑Other (list)_____

Cavities:
Does subject have a history of cavities: ❑Yes ❑No ❑Unknown

VII. OPHTHALOMOGY

Has subject ever been evaluated by ophthalmologist for TSC finding: ❑Yes ❑No ❑Unknown
If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by ophthalmologist: ❑Yes ❑No ❑Unknown

RETINAL FINDINGS

Retinal Findings: ❑Yes ❑No ❑Unknown
If yes, complete this section. If No or Unknown, skip to the Non-Retinal Findings (this section).

Hamartoma: ❑Yes ❑No ❑Unknown
--Mulberry lesion: ❑Yes ❑No ❑Unknown
If yes, indicate location: ❑Right ❑Left ❑Bilateral ❑Unknown

Symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Visual loss
❑Pain
❑Hemorrhage
Other (list) _____
Treatment: ❑Yes ❑No ❑Unknown
If yes, indicate what treatment was performed (choose all that apply):
❑Photocoagulation
❑Radiation
❑Enucleation
❑Other (list) _____

--Flat smooth-surfaced lesion: ❑Yes ❑No ❑Unknown
If yes, indicate location: ❑Right ❑Left ❑Bilateral ❑Unknown

Symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Visual loss
Other (list) _____
Treatment: ❑Yes ❑No ❑Unknown
If yes, indicate what treatment was performed: _____

--Mixed mulberry/flat smooth-surfaced lesion: ❑Yes ❑No ❑Unknown
If yes, indicate location: ❑Right ❑Left ❑Bilateral ❑Unknown

Symptoms: ❑Yes ❑No ❑Unknown

If yes, indicate which symptom(s) present (choose all that apply):
- ❑Visual loss
- ❑Pain
- ❑Hemorrhage
- Other (list) _____

Treatment: ❑Yes ❑No ❑Unknown

If yes, indicate what treatment was performed (choose all that apply):
- ❑Photocoagulation
- ❑Radiation
- ❑Enucleation
- ❑Other (list) _____

Achromic Patch: ❑Yes ❑No ❑Unknown
If yes, indicate location: ❑Right ❑Left ❑Bilateral ❑Unknown

Vascular Changes: ❑Yes ❑No ❑Unknown
If yes, indicate location: ❑Right ❑Left ❑Bilateral ❑Unknown

Optic Nerve Atrophy: ❑Yes ❑No ❑Unknown
If yes, indicate location: ❑Right ❑Left ❑Bilateral ❑Unknown

Papilledema: ❑Yes ❑No ❑Unknown
If yes, indicate location: ❑Right ❑Left ❑Bilateral ❑Unknown
Is this related to Hydrocephalus: ❑Yes ❑No ❑Unknown *(If yes, complete the section found under the Neurology heading)*
List details of signs, symptoms and treatments: _____
_____

Visual Field Defects: ❑Yes ❑No ❑Unknown
If yes, indicate location: ❑Right ❑Left ❑Bilateral ❑Unknown
Is cause for visual defect known: ❑Yes ❑No ❑Unknown
If yes, list: _____
Has subject been prescribed vigabatrin: ❑Yes ❑No ❑Unknown
If yes: ❑Used in the past ❑Currently used
Duration of vigabatrin therapy: _____ month(s) _____ year(s)

NON-RETINAL FINDINGS

Non-retinal Findings: ❑Yes ❑No ❑Unknown
If yes, indicate the finding (choose all that apply)
❑Strabismus ❑Right ❑Left ❑Bilateral ❑Unknown
❑Other (list) _____

VIII. CARDIOLOGY

Has subject ever been evaluated by cardiologist for TSC finding: ❑Yes ❑No ❑Unknown
If yes, ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by cardiologist: ❑Yes ❑No ❑Unknown

ELECTROCARDIOGRAM

Has subject had an electrocardiogram (EKG): ❑Yes ❑No ❑Unknown
If yes, what was subject's age at most recent exam: _____ month(s) _____ year(s)
What were the results:
- ❑Unknown
- ❑Normal
- ❑Arrhythmia present (list) _____
- ❑Other (list) _____

Did subject have symptoms related to abnormality found by EKG: ❑Yes ❑No ❑Unknown

If yes, indicate which symptom(s) present (choose all that apply):
- ❑Tachycardia
- ❑Irregular heart rhythm
- ❑Shortness of breath
- ❑Other (list) _____

Were symptoms related to EKG abnormality treated: ❑Yes ❑No ❑Unknown

If yes, what treatment was performed (choose all that apply):
- ❑Medication (list current medication) _____
- ❑Ablation: _____ month(s) _____ year(s)
- ❑Other (list) _____

CARDIAC IMAGING

Echocardiogram

Was prenatal high-resolution echocardiogram performed: ❑Yes ❑No ❑Unknown

If yes, indicate the result:
- ❑Unknown
- ❑Normal
- ❑Abnormal
- ❑Rhabdomyomata
- ❑Other abnormalities (list) _____

Has subject had an echocardiogram post birth: ❑Yes ❑No ❑Unknown

If yes, what was subject's age at most recent exam: _____ month(s) _____ year(s)

OTHER CARDIAC IMAGING

Has subject had any of the following imaging studies performed (choose all that apply):

Study	Subject's age at most recent exam Month(s) / year(s)
❑Chest X-ray	_____ / _____
❑Chest CT	_____ / _____
❑Chest MRI	_____ / _____
❑Other (list)_____	_____ / _____

_____

If any of the above imaging studies were performed, complete the following section. If not, skip to section IX (Pulmonology)

CARDIAC FINDINGS

- ❑Unknown
- ❑Normal

If normal, how was result found: ❑Echocardiogram ❑Chest x-ray ❑CT ❑MRI ❑Other_____

- ❑Abnormal

If abnormal, check all that apply:
- ❑Rhabdomyomata Result found by: ❑Echocardiogram ❑Chest x-ray ❑CT ❑MRI ❑Other_____
- ❑Coarctation of aorta Result found by: ❑Echocardiogram ❑Chest x-ray ❑CT ❑MRI ❑Other_____
- ❑Cardiac enlargement Result found by: ❑Echocardiogram ❑Chest x-ray ❑CT ❑MRI ❑Other_____
- ❑Other (list) _____

If any cardiac findings were identified above, complete the following section. If not, skip to section IX (Pulmonology)

Rhabdomyomata: ❑Yes ❑No ❑Unknown

If yes, when was the finding discovered: ❑Prenatal ❑Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: ❑Echocardiogram ❑CT ❑MRI ❑Other_____

Location/Quantity/Size (provide as much detail as possible based on most recent and best quality imaging study):

	Total no. of lesions	Size and number in each range <0.5 cm	0.5-1.0 cm	1.1-2.5 cm	>2.5cm
❑RA*	_____	_____	_____	_____	_____
❑RV*	_____	_____	_____	_____	_____
❑LA*	_____	_____	_____	_____	_____
❑LV*	_____	_____	_____	_____	_____
❑AS*	_____	_____	_____	_____	_____
❑VS*	_____	_____	_____	_____	_____

* RA-right atrium, RV-right ventricle, LA-left atrium, LV-left ventricle, AS-atrial septum, VS-ventricular septum

Did subject have symptoms related to rhabdomyomata: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Arrhythmia
❑Cardiomegaly
❑Heart failure
❑Other (list)_____
Treatment related to rhabdomyomata: ❑Yes ❑No ❑Unknown
If yes, what treatment was performed (choose all that apply):
❑Medication
❑Surgical resection
❑Other (list)_____
Was tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA):
❑Yes ❑No ❑Unknown
If yes, indicate location of bank and physician who banked the sample:_____

Coarctation of aorta: ❑Yes ❑No ❑Unknown
If yes, when was the finding discovered: ❑Prenatal ❑Post birth
Subject's age at time of discovery was _____ month(s) _____ year(s)
Result found by: ❑Echocardiogram ❑CT ❑MRI ❑Other_____
Did subject have symptoms related to coarctation of aorta: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Cardiomegaly
❑Hypertension
❑Other (list)_____
Treatment related to coarctation of aorta: ❑Yes ❑No ❑Unknown
If yes, what treatment was performed (choose all that apply):
❑Surgical resection
❑Other (list)_____

Other cardiovascular abnormalities: ❑Yes ❑No ❑Unknown
If yes, were any other cardiovascular abnormalities found: ❑Yes ❑No ❑ Unknown
If yes, list abnormalities found: _____
If yes, when was the finding discovered: ❑Prenatal ❑Post birth
Subject's age at time of discovery was _____ month(s) _____ year(s)
Result found by: ❑Echocardiogram ❑Chest X-ray ❑CT ❑MRI ❑Other _____
Did subject have symptoms related to other abnormality: ❑Yes ❑No ❑Unknown
❑If yes, list_____
Did subject have treatment related to other abnormality: ❑Yes ❑No ❑Unknown
❑If yes, list:_____

IX. PULMONOLOGY

Has subject ever been evaluated by pulmonologist for TSC finding: ❑Yes ❑No ❑Unknown
If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by pulmonologist: ❑Yes ❑No ❑Unknown

RELEVANT PULMONARY HISTORY

Does subject have any chronic pulmonary disorders not necessarily related to TSC: ❑Yes ❑No ❑Unknown
If yes, indicate all that apply:
❑Asthma
❑Emphysema
❑Other (list)_____

Did subject have pulmonary signs or symptoms: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑None ❑Shortness of breath
❑Cough ❑Wheezing
❑Chest pain ❑Pneumothorax
❑Chylothorax
❑Other (list)_____

Has subject ever habitually smoked: ❑Yes ❑No ❑Unknown
If yes, indicate how many years subject smoked: _____ years
What substance did subject smoke: ❑Cigarettes ❑Cigars ❑Pipe ❑Other _____
Does subject currently smoke: ❑Yes ❑No ❑Unknown
If no, what is interval since last use: _____ month(s) _____ year(s)
How much does subject smoke and how often:
❑Cigarettes How many/day: _____
❑Pipe How many/day: _____
❑Cigars How many/day: _____
❑Other How many/day: _____

Pregnancy: ❑Yes ❑No ❑Unknown ❑N/A
If yes, Number of pregnancies: _____

Has subject reached menopause: ❑Yes ❑No ❑Unknown ❑N/A

Has subject undergone a hysterectomy: ❑Yes ❑No ❑Unknown ❑N/A
If yes, when was surgery performed: _____ year

Has subject undergone an Oophorectomy: ❑Yes ❑No ❑Unknown ❑N/A
If yes, when was surgery performed: _____ year

Hormone therapy (including birth control substances): ❑Yes ❑No ❑Unknown ❑N/A
❑Estrogen: _____ years taken
If yes, is subject currently taking Estrogen: ❑Yes ❑No ❑Unknown
If no, what is interval since last use: _____ month(s) _____ year(s)
❑Progesterone: _____ years taken
If yes, is subject currently taking Progesterone: ❑Yes ❑No ❑Unknown
If no, what is interval since last use: _____ month(s) _____ year(s)
❑Other (list):_____
_____

Does subject have a family history of pulmonary disease: ❑Yes ❑No ❑Unknown
If yes, give details:_____
_____

PULMONARY PHYSICAL EXAM

Does subject have any of the following:
❑Wheezes
❑Crackles

❑Clubbing of digits
❑Other (list)_____

PULMONARY LABS/STUDIES

(Provide most current lab values for all that apply:)

Test	Values	Date of most recent test results month / year
Pulmonary function test:	❑Tested ❑Not tested	
FEV_1	_____	_____ / _____
FVC	_____	_____ / _____
DLCO	_____	_____ / _____
Arterial blood gasses	❑Tested ❑Not tested	
PaO_2	_____mmHg	_____ / _____
$PACO_2$	_____mmHg	_____ / _____
pH	_____	_____ / _____
Hemoglobin oxygen saturation test:	❑Tested ❑Not tested	
$Sa\ O_2$	_____%	_____ / _____

PULMONARY DIAGNOSTICS

Has subject had any of the following diagnostic studies performed (choose all that apply):

Study	What was subject's age at most recent exam month(s) / year(s)
❑X-ray-Chest	_____ / _____
❑High resolution CT-Chest	_____ / _____
❑CT-Chest	_____ / _____
❑MRI	_____ / _____
❑Pulmonary Function Test (PFT)	_____ / _____
❑Biopsy-bronchoscopic	_____ / _____
❑Biopsy-surgical	_____ / _____
❑Other (list)_____	_____ / _____
_____	_____ / _____
_____	_____ / _____

If any of the above diagnostic studies were performed, complete the following section. If not, skip to section X (Renal)

PULMONARY FINDINGS

If any of the above imaging studies were performed, what were the results: (choose all that apply)

❑Unknown
❑Normal
If normal, how was result found: ❑X-ray ❑High resolution CT ❑CT ❑MRI ❑PFT ❑Biopsy-bronchoscopic ❑Biopsy, surgical ❑Other (list) _____
❑Abnormal
If abnormal, check all that apply:
❑Cystic lesions consistent with lymphangiomyomatosis (LAM)
Result found by: ❑X-ray ❑High resolution CT ❑CT ❑MRI ❑PFT ❑Biopsy-bronchoscopic ❑Biopsy, surgical ❑Other (list) _____
❑Multifocal micronodular pneumocyte hyperplasia (MMPH)
Result found by: ❑X-ray ❑High resolution CT ❑CT ❑MRI ❑PFT ❑Biopsy-bronchoscopic ❑Biopsy, surgical ❑Other (list) _____
❑Other (list) _____

Subject name: First, Middle, Last _____ **DOB:**_____

If any of the above pulmonary abnormalities were identified, complete the following section. If not, skip to section X (Renal).

Cystic lesions/LAM: ❑Yes ❑No ❑Unknown
If yes, subject's age at time of discovery: _____ month(s) _____ year(s)
Result found by: ❑X-ray ❑High resolution CT ❑CT ❑MRI ❑PFT ❑Biopsy-bronchoscopic ❑Biopsy-surgical
❑Other_____
Pathology comments, if relevant: _____
Location (based on most recent and best quality imaging study): ❑Right ❑Left ❑Bilateral
Were any treatments performed: ❑Yes ❑No ❑Unknown
If yes, choose the treatment performed:
❑Inhaler: List type _____ ❑PRN use ❑Scheduled use
❑O_2 supplementation: ❑PRN use ❑Scheduled use
❑Progesterone therapy
❑Lung transplant
❑Hysterectomy/oophorectomy
❑Chest tube placement: ❑Right ❑Left ❑Bilateral
❑Chylous fluid drainage: ❑Right ❑Left ❑Bilateral
❑Pleurodesis: ❑Right ❑Left ❑Bilateral
❑Chest surgery: ❑Right ❑Left ❑Bilateral
❑Other (list)_____

MMPH (Multifocal multinodular pneumocyte hyperplasia): ❑Yes ❑No ❑Unknown
If yes, subject's age at time of discovery: _____ month(s) _____year(s)
Result found by: ❑X-ray ❑High-resolution CT ❑CT ❑MRI ❑PFT ❑Biopsy ❑Other_____
Pathology comments, if relevant: _____
Location (based on most recent and best quality imaging study): ❑Right ❑Left ❑Bilateral

Other Findings: ❑Yes ❑No ❑Unknown
If yes, list finding: _____
Subject's age at time of discovery: _____ month(s) _____ year(s)
Result found by: ❑X-ray ❑High-resolution CT ❑CT ❑MRI ❑PFT ❑Biopsy ❑Other_____
Pathology comments, if relevant: _____

Did subject have signs or symptoms related to other abnormal pulmonary findings: ❑Yes ❑No ❑Unknown
If yes, list findings: _____

Were any treatments related to other abnormal pulmonary findings: ❑Yes ❑No ❑Unknown
If yes, list: _____

X. RENAL

Has subject ever been evaluated by nephrologist for TSC finding: ❑Yes ❑No ❑Unknown
If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by nephrologist: ❑Yes ❑No ❑Unknown

Has subject ever been evaluated by urologist for TSC finding: ❑Yes ❑No ❑Unknown
If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by urologist: ❑Yes ❑No ❑Unknown

RENAL PHYSICAL EXAM

Does subject have a palpable mass: ❑Yes ❑No ❑Unknown
If yes: ❑Right ❑Left ❑Bilateral ❑Unknown

Does subject have any other relevant physical findings (list)_____

Subject name: First, Middle, Last _____ **DOB:**_____

RENAL LABS
(Provide most current lab values)

Labs		Values	Date of most recent test results month(s) / year(s)
❑Creatinine	❑Not tested	_____	_____ / _____
❑BUN	❑Not tested	_____	_____ / _____
❑Urine protein	❑Not tested	❑1+ ❑2+ ❑3+ ❑4+	_____ / _____
❑Hematuria	❑Not tested	❑Trace ❑Small ❑Medium ❑Large	_____ / _____

RENAL DIAGNOSTICS

Has subject had any of the following diagnostic studies performed (choose all that apply):

Study	What was subject's age at most recent exam month(s) / year(s)
❑Ultrasound – Renal/Abdominal	_____ / _____
❑CT – Renal/Abdominal	_____ / _____
❑MRI	_____ / _____
❑Angiogram	_____ / _____
❑Nuclear study	_____ / _____
❑Biopsy	_____ / _____
❑Volumetric analysis of renal lesions	_____ / _____
❑Other (list)_____	

If any of the above diagnostic studies were performed, complete the following section. If not, skip to section XI (Neurology).

RENAL FINDINGS

❑Unknown

		Results found by: Ultrasound	CT	MRI	Angiogram	Nuclear study	Other (list)
❑Normal		❑	❑	❑	❑	❑	❑_____
Kidney Size		❑	❑	❑	❑	❑	❑_____
Right:	Length _____cm	Width _____cm		Thickness _____cm			
Left:	Length _____cm	Width _____cm		Thickness _____cm			
❑Abnormal:							
❑Cystic lesions		❑	❑	❑	❑	❑	❑_____
❑Angiomyolipoma (AML)		❑	❑	❑	❑	❑	❑_____
❑Other solid tumor		❑	❑	❑	❑	❑	❑_____
❑Abnormal renal vasculature		❑	❑	❑	❑	❑	❑_____
❑Other: _____		❑	❑	❑	❑	❑	❑_____

If any of the above abnormalities were found, complete the following section. If not, skip to section XI (Neurology).

Cystic lesions: ❑Yes ❑No ❑Unknown
If yes, when was the finding discovered: ❑Prenatal ❑Post birth
Subject's age at time of discovery was _____ month(s) _____ year(s)
Result found by: ❑Ultrasound ❑CT ❑MRI ❑Angiogram ❑Nuclear study ❑Other_____

Location/Quantity/Size (provide as much detail as possible based on most recent and best quality imaging study):
❑Right Total number of lesions: ❑1-3 ❑4-10 ❑>10 Size of largest cyst: _____ cm or ❑Undetermined size
❑Left Total number of lesions: ❑1-3 ❑4-10 ❑>10 Size of largest cyst: _____ cm or ❑Undetermined size

Has subject ever had lesion which is no longer evident: ❑Yes ❑No ❑Unknown
Radiology comments, if relevant: _____

Did subject have symptoms related to cystic lesions: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Elevated blood pressure
❑Hematuria
❑Pain
❑Impaired renal function
❑Other (list)_____

Were any treatments related to cystic lesions performed: ❑Yes ❑No ❑Unknown
If yes, what treatment was performed (choose all that apply):
❑Surgical resection: ❑Right ❑Left ❑Bilateral
❑Nephrectomy: ❑Right ❑Left ❑Bilateral
❑Dialysis
❑Renal transplantation
❑Other (list)_____

Was tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA):
❑Yes ❑No ❑Unknown
If yes, indicate location of bank and physician who banked sample:_____

Angiomyolipoma (AML): ❑Yes ❑No ❑Unknown
If yes, when was the finding discovered: ❑Prenatal ❑Post birth
Subject's age at time of discovery was _____ month(s) _____ year(s)
Result found by: ❑Ultrasound ❑CT ❑MRI ❑Angiogram ❑Nuclear study ❑Biopsy ❑ Other _____
Pathology comments, if relevant: _____

Location/Quantity/Size (provide as much detail as possible based on most recent and best quality imaging study):
❑Right Total number of lesions: ❑1-3 ❑4-10 ❑>10 Size of largest AML: _____ cm or ❑Undetermined size
❑Left Total number of lesions: ❑1-3 ❑4-10 ❑>10 Size of largest AML: _____ cm or ❑Undetermined size

Did subject have symptoms related to AML: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Elevated blood pressure ❑Hematuria ❑Pain ❑Impaired renal function
❑Other (list)_____

Were any treatments related to AML performed: ❑Yes ❑No ❑Unknown
If yes, what treatment was performed (choose all that apply):
❑Surgical resection: ❑Right ❑Left ❑Bilateral
❑Nephrectomy: ❑Right ❑Left ❑Bilateral
❑Dialysis
❑Renal transplantation
❑Other (list)_____

Was tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA):
❑Yes ❑No ❑Unknown
If yes, indicate location of bank and physician who banked sample: _____

Other solid tumor: ❑Yes ❑No ❑Unknown
If yes, when was the finding discovered: ❑Prenatal ❑Post birth
Subject's age at time of discovery was _____ month(s) _____ year(s)
Result found by: ❑Ultrasound ❑CT ❑MRI ❑Angiogram ❑Nuclear study ❑Biopsy
❑Other _____
Pathology comments, if relevant: _____

Location/Quantity/Size (provide as much detail as possible based on most recent and best quality imaging study):
❑Right Total number of lesions: ❑1-3 ❑4-10 ❑>10 Size of largest tumor: _____ cm or ❑Undetermined size
❑Left Total number of lesions: ❑1-3 ❑4-10 ❑>10 Size of largest tumor: _____ cm or ❑Undetermined size

Did subject have symptoms related to other solid tumor: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Elevated blood pressure
❑Hematuria
❑Pain
❑Impaired renal function
❑Hemorrhage
❑Other (list)_____

Were any treatments related to AML performed: ❑Yes ❑No ❑Unknown
If yes, what treatment was performed (choose all that apply):
❑Surgical resection: ❑Right ❑Left ❑Bilateral
❑Nephrectomy: ❑Right ❑Left ❑Bilateral
❑Dialysis
❑Chemotherapy
❑Renal transplantation
❑Other (list)_____

Abnormal renal vasculature: ❑Yes ❑No ❑Unknown
If yes, when was the finding discovered: ❑Prenatal ❑Post birth
Subject's age at time of discovery was _____ month(s) _____ year(s)
Result found by: ❑Ultrasound ❑CT ❑MRI ❑Angiogram ❑Nuclear study ❑ Other _____
Location of abnormal renal vasculature: ❑Right ❑Left ❑Bilateral

Was abnormal renal vasculature found: ❑Yes ❑No ❑Unknown
If yes, indicate type of finding (choose all that apply):
❑Aneurysm
❑Arteriovenous malformation
❑Arterial dilatation
❑Other (list)_____

Did subject have symptoms related to abnormal renal vasculature: ❑Yes ❑No ❑Unknown
If yes, indicate which symptom(s) present (choose all that apply):
❑Elevated blood pressure
❑Hematuria
❑Pain
❑Impaired renal function
❑Hemorrhage
❑Other (list)_____

Were any treatments related to abnormal renal vasculature performed: ❑Yes ❑No ❑Unknown
If yes, what treatment was performed (choose all that apply):
❑Surgical resection: ❑Right ❑Left ❑Bilateral
❑Embolization: ❑Right ❑Left ❑Bilateral
❑Nephrectomy
❑Other (list)_____

XI. NEUROLOGY

Has subject ever been evaluated by neurologist for TSC finding: ❑Yes ❑No ❑Unknown
If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by neurologist: ❑Yes ❑No ❑Unknown

Has subject ever been evaluated by epileptologist for TSC finding: ❑Yes ❑No ❑Unknown
If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by epileptologist: ❑Yes ❑No ❑Unknown

Has subject ever been evaluated by neurosurgeon for TSC finding: ❑Yes ❑No ❑Unknown

If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by neurosurgeon: ❑Yes ❑No ❑Unknown

Has subject ever been evaluated by psychiatrist for TSC finding: ❑Yes ❑No ❑Unknown
If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by psychiatrist: ❑Yes ❑No ❑Unknown

Has subject ever been evaluated by psychologist/neuropsychologist for TSC finding: ❑Yes ❑No ❑Unknown
If yes: ❑for diagnostic purposes ❑for treatment ❑for both
Is subject currently followed by psychologist/neuropsychologist: ❑Yes ❑No ❑Unknown

NEUROLOGIC PHYSICAL EXAM *(list abnormal findings only)*

Cranial nerves:
❑Papilledema
❑Visual field defect
❑Eye movement abnormalities
❑Other (list)_____

Motor:
❑Focal weakness
❑Monoparesis affecting: ❑R upper ❑R lower ❑L upper ❑L lower
❑Hemiparesis affecting: ❑R upper ❑R lower ❑L upper ❑L lower
❑Quadriparesis

Tone:
❑Spasticity
❑Rigidity
❑Hypotonia

Abnormal movements:
❑Dystonia
❑Chorea/athetosis
❑Tremor

Coordination:
List limb and finding: _____

Sensory:
List finding: _____

Reflexes:
❑Absent
❑Hypoactive
❑Hyperactive
❑Babinski: ❑Unilateral ❑Bilateral

Gait:
❑Nonambulatory
❑Hemiparesis
❑Diplegia

Subject name: First, Middle, Last _____ **DOB:**_____

BRAIN

BRAIN DIAGNOSTICS (NEUROIMAGING)

Has subject had any of the following imaging studies performed (choose all that apply):

Study	If yes, what was subject's age at most recent exam? Month(s) / year(s)	
❑CT – Head	_____ / _____	
❑MRI - Head	_____ / _____	
❑MR Angiography (MRA)	_____ / _____	
❑PET Scan – Standard	_____ / _____	
❑AMT – PET scan	_____ / _____	(alpha-[11C]methyl-L-tryptophan-PET Scan)
❑SPECT	_____ / _____	
❑Other (list)_____	_____ / _____	
_____		

If any of the above diagnostic studies were performed, complete the following section. If not, skip to the Epilepsy part of section XI (Neurology).

BRAIN FINDINGS

❑Unknown

	Results found by CT	MRI	MRA	PET-Standard	AMT-PET	SPECT	Other
❑Normal	❑	❑	❑	❑	❑	❑	❑_____
❑Abnormal	❑	❑	❑	❑	❑	❑	❑_____
❑Tubers	❑	❑	❑	❑	❑	❑	❑_____
❑Radial glial white matter lesions	❑	❑	❑	❑	❑	❑	❑_____
❑Subependymal nodules (SEN)	❑	❑	❑	❑	❑	❑	❑_____
❑Subependymal giant-cell astrocytoma (SEGA)	❑	❑	❑	❑	❑	❑	❑_____
❑Other _____	❑	❑	❑	❑	❑	❑	❑_____
❑Other _____	❑	❑	❑	❑	❑	❑	❑_____

If any of the above abnormal findings were identified, complete the following section. If not, skip to the Epilepsy part of section XI (Neurology).

❑**Tubers**

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: ❑CT ❑MRI ❑Other_____

Location/Quantity/Size (include **ONLY** information on tubers identified by T2 or FLAIR MRI imaging):

Location	no. of lesions	Size and number in each range <1.5 cm	1.5-3.0 cm	>3.0cm	Lesion type (choose all that apply) Cortical	Subcortical	Cortical extending to subcortical
Frontal							
❑Right	_____	_____	_____	_____	❑	❑	❑
❑Left	_____	_____	_____	_____	❑	❑	❑
Parietal							
❑Right	_____	_____	_____	_____	❑	❑	❑
❑Left	_____	_____	_____	_____	❑	❑	❑
Temporal							
❑Right	_____	_____	_____	_____	❑	❑	❑
❑Left	_____	_____	_____	_____	❑	❑	❑

Occipital						
❑Right	_____	_____	_____	_____	❑	❑	❑
❑Left	_____	_____	_____	_____	❑	❑	❑
Cerebellar						
❑Right	_____	_____	_____	_____	❑	❑	❑
❑Left	_____	_____	_____	_____	❑	❑	❑
Diencephalon						
❑Right	_____	_____	_____	_____	❑	❑	❑
❑Left	_____	_____	_____	_____	❑	❑	❑
Brain stem						
❑Right	_____	_____	_____	_____	❑	❑	❑
❑Left	_____	_____	_____	_____	❑	❑	❑

Other: _____

_____

❑**Radial glial white matter lesions**

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: ❑MRI ❑Other (list) _____

Location: ❑Right hemisphere ❑Left hemisphere

❑**Subependymal nodules (SEN) (lesions < 1 cm)**

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: ❑CT ❑MRI ❑Other (list) _____

Location/Quantity/Size:

		Size and # in each range	
Location	Total # of lesions	<0.5 cm	0.5-0.9 cm
❑Right lateral ventricle	_____	_____	_____
❑Left lateral ventricle	_____	_____	_____

❑**Subependymal giant cell astrocytoma (SEGA) (lesions 1 cm or larger)**

When was the finding discovered: ❑Prenatal ❑Post birth

Subject's age at time of discovery was _____ month(s) _____ year(s)

Result found by: ❑CT ❑MRI ❑Other _____

Location/Quantity/Size:

		Size and # in each range			
Location	Total # of lesions	1.0-2.0 cm	2.1-3.0 cm	3.1-5.0 cm	>5.0 cm
❑Right frontal horn	_____	_____	_____	_____	_____
❑Left frontal horn	_____	_____	_____	_____	_____
❑Right posterior lateral ventricle	_____	_____	_____	_____	_____
❑Left posterior lateral ventricle	_____	_____	_____	_____	_____

Did subject have symptoms related to SEGA: ❑Yes ❑No ❑Unknown

If yes, indicate which symptom(s) present (choose all that apply):

- ❑Hydrocephalus
- ❑Ventriculomegaly
- ❑Headaches
- ❑Increased seizures
- ❑Visual impairment
- ❑Eye movement abnormalities
- ❑Neuroendocrine dysfunction
- ❑Behavioral disturbances
- ❑Sleep disorders
- ❑Other (list) _____

Were any treatments related to SEGA performed: ❑Yes ❑No ❑Unknown

If yes, what treatment was performed (choose all that apply):

- ❑ Surgical resection: Number of times surgery performed _____
  - Location of lesion resected:

❑Right frontal horn ❑Left frontal horn ❑Right posterior ventricle ❑Left posterior ventricle
Lesion size at time of surgery _____
Was subject symptomatic at time of surgery: ❑Yes ❑No ❑Unknown
What was extent of resection: ❑Total ❑Partial
If partial, what was size of residual SEGA post surgery:
❑1.0-2.0 cm ❑2.1-3.0 cm ❑3.1-5.0 cm ❑>5.0 cm
❑ Other (list)_____

Was blood or tissue banked outside the context of formal research project (e.g. TSC Tissue Donation Program at TSA):
❑Yes ❑No ❑Unknown
If yes, indicate location of bank and physician who banked sample:_____

Were there surgical complications related to SEGA: ❑Yes ❑No ❑Unknown
If yes, indicate which complication(s) present (choose all that apply):
❑Memory loss
❑Need for ventricular shunt
❑Gait disturbance
❑Syndrome of inappropriate ADH (SIADH)
❑Other (list) _____

Has there been regrowth of SEGA at operative site: ❑Yes ❑No ❑Unknown
If there have been multiple surgeries, was surgery for (choose all that apply):
❑Reduction of same lesion
❑Regrowth of same lesion
❑Resection of new/different lesion

Has there been malignant transformation related to SEGA: ❑Yes ❑No ❑Unknown
If yes, provide details of tumor type and treatment, if known: _____
_____

EPILEPSY

Has subject ever had seizures: ❑Yes ❑No ❑Unknown
If yes, continue with this part of Section XI (Neurology). If No or Unknown, skip to the Sleep part of Section XI (Neurology)

Has subject ever had infantile spasms: ❑Yes ❑No ❑Unknown
If yes, continue with this part of Section XI (Neurology). If No or Unknown, skip to Current Seizure History part of Section XI (Neurology), if appropriate.

Infantile Spasms

Does subject currently have infantile spasms: ❑Yes ❑No ❑Unknown
Subject's age of onset: _____ month(s) _____ year(s) ❑Unknown
Seizure cluster duration: ❑<1 min. ❑1-<2 min. ❑2-<5 min. ❑5-10 min. ❑>10 min.
Seizure cluster frequency (check all that apply):

Current Seizure Frequency	Greatest Seizure Frequency
❑ History of <3 seizures/lifetime	❑ History of <3 seizures/lifetime
❑ Seizure free, requires antiepileptic drug or treatment	❑ 1 – 3 seizures/year
❑ 1 – 3 seizures/year	❑ 4 – 11 seizures/year
❑ 4 – 11 seizures/year	❑ 1 – 3 seizures/month
❑ 1 – 3 seizures/month	❑ 1 – 6 seizures/week
❑ 1 – 6 seizures/week	❑ 1 or more seizures/day
❑ 1 or more seizures/day	

Current treatment for infantile spasms (check all that apply and list medication or treatment where appropriate):
❑Single medication _____
❑Medication combination _____
❑Vagus nerve stimulator (VNS)

❑Ketogenic diet
❑Epilepsy surgery (*if checked, complete the separate Surgery section*)
❑Other (list)_____

Most effective treatment for infantile spasms (check all that apply and list medication or treatment where appropriate):
❑Single medication _____
❑Medication combination _____
❑Vagus nerve stimulator (VNS)
❑Ketogenic diet
❑Epilepsy surgery (*if checked, complete the separate Surgery section*)
❑Other (list)_____

Prior history of infantile spasms
Has subject ever had infantile spasms which have resolved: ❑Yes ❑No ❑Unknown
Age of onset: _____ month(s) _____ year(s) ❑Unknown
Age of cessation: _____ month(s) _____ year(s) ❑Unknown

Most effective treatment for infantile spasms: _____
_____

Current Seizure History
Does subject currently have seizures: ❑Yes ❑No ❑Unknown
If yes, continue with this part of Section XI (Neurology). If No or Unknown, skip to Prior Seizure History.

Current seizure type:

Generalized Seizures	Partial Seizures
❑Tonic clonic seizures (TC)	❑Simple partial sensory (SPS
❑Tonic seizures (T)	❑Simple partial motor (SPM)
❑Clonic seizures (C)	❑Complex partial seizures (CPS)
❑Myoclonic seizures (M)	❑Secondary generalized seizures (SG)
❑Atonic seizures (A)	❑Gelastic seizures (G)
❑Atypical absence seizures (AA)	❑Other (PO) (list)_____
❑Typical absence seizures (TA)	_____
❑Other (GO) (list): _____	
_____	

Other seizures
❑Febrile seizures (F)
❑Other (OO) (list)_____

Age of onset for current seizure type (use above abbreviation for seizure type). List all that apply:

Age of Onset				Seizure duration				
Seizure Type	*Month(s)*	*Year(s)*	*Unknown*	*<1 min*	*<2 min*	*<5 min*	*5-10 min*	*>10 min*
_____	_____	_____	❑	❑	❑	❑	❑	❑
_____	_____	_____	❑	❑	❑	❑	❑	❑
_____	_____	_____	❑	❑	❑	❑	❑	❑
_____	_____	_____	❑	❑	❑	❑	❑	❑
_____	_____	_____	❑	❑	❑	❑	❑	❑
_____	_____	_____	❑	❑	❑	❑	❑	❑

Frequency of seizures:

Current Seizure Frequency	Greatest Seizure Frequency
❑History of <3 seizures/lifetime	❑History of <3 seizures/lifetime
❑Seizure free, requires antiepileptic drug or treatment	❑1 – 3 seizures/year
❑1 – 3 seizures/year	❑4 – 11 seizures/year
❑4 – 11 seizures/year	❑1 – 3 seizures/month
❑1 – 3 seizures/month	❑1 – 6 seizures/week

❑1 – 6 seizures/week ❑1 or more seizures/day
❑1 or more seizures/day

Longest seizure-free duration (list) : _____ months _____ year(s)

Current treatment (check all that apply and list medication or treatment where appropriate):
❑Single medication _____
❑Medication combination _____
❑Vagus nerve stimulator (VNS)
❑Ketogenic diet
❑Epilepsy surgery (*if checked, complete the separate Surgery section*)
❑Other (list)_____

Most effective treatment for infantile spasms (check all that apply and list medication or treatment where appropriate):
❑Single medication _____
❑Medication combination _____
❑Vagus nerve stimulator (VNS)
❑Ketogenic diet
❑Epilepsy surgery (*if checked, complete the separate Surgery section*)
❑Other (list)_____

Prior seizure history

Has subject ever had a prior seizure type which has resolved: ❑Yes ❑No ❑Unknown
If yes, list prior seizure type (use abbreviation list found under 'Current Seizure Type' page 21. List all that apply):

Seizure type	Age of onset Month(s)/Year(s)	Unknown	Age of cessation Month(s)/Year(s)	Unknown
_____	_____/_____	❑	_____/_____	❑
_____	_____/_____	❑	_____/_____	❑
_____	_____/_____	❑	_____/_____	❑
_____	_____/_____	❑	_____/_____	❑
_____	_____/_____	❑	_____/_____	❑
_____	_____/_____	❑	_____/_____	❑

Most effective treatment for prior seizure type (check all that apply and list medication or treatment where appropriate):
❑Single medication _____
❑Medication combination _____
❑Vagus nerve stimulator (VNS)
❑Ketogenic diet
❑Epilepsy surgery (*if checked, complete the separate Surgery section*)
❑Other (list)_____

Status Epilepticus

Has subject ever had status epilepticus (SE): ❑Yes ❑No ❑Unknown
If yes, number of occurrences: _____
Number of emergency room (ER) visits due to SE (lifetime): _____
Number of hospitalizations due to SE (lifetime): _____

Past Medical Treatments

Medications (check all that apply):

Medications	Reason for discontinuation of medication: Adverse effect	Lack of efficacy	Seizure Remission
❑ACTH	❑	❑	❑
❑Carbamazepine	❑	❑	❑
❑Clonazepam	❑	❑	❑
❑Clorazepate	❑	❑	❑
❑Diazepam	❑	❑	❑

❑Ethosuximide	❑	❑	❑
❑Felbamate	❑	❑	❑
❑Gabapentin	❑	❑	❑
❑Lamotrigine	❑	❑	❑
❑Levetiracetam	❑	❑	❑
❑Lorazepam	❑	❑	❑
❑Oxcarbazepine	❑	❑	❑
❑Phenobarbital	❑	❑	❑
❑Phenytoin	❑	❑	❑
❑Prednisone	❑	❑	❑
❑Primidone	❑	❑	❑
❑Tiagabine	❑	❑	❑
❑Topiramate	❑	❑	❑
❑Valproic acid	❑	❑	❑
❑Vigabatrin	❑	❑	❑
❑Vitamin B_6	❑	❑	❑
❑Zonisamide	❑	❑	❑
❑Other: _____	❑	❑	❑
❑Other: _____	❑	❑	❑
❑Other: _____	❑	❑	❑

Other past treatments (check all that apply):

❑Vagus nerve stimulator (VNS)
Reason discontinued: ❑Adverse effect ❑Lack of efficacy ❑Seizure remission
Date VNS inactivated: _____ Date VNS removed: _____
Total length of treatment: _____ month(s) _____ year(s)

❑Ketogenic diet
Reason discontinued: ❑Adverse affect ❑Lack of efficacy ❑Seizure remission
Total length of treatment: _____ month(s) _____ year(s)

Epilepsy Surgery

Has subject had epilepsy surgery: ❑Yes ❑No ❑Unknown
If yes, continue with this part of Section XI (Neurology). If No or Unknown, skip to Sleep part of Section XI (Neurology).

Age at time of surgery: _____ month(s) _____ year(s) ❑Unknown
Type of surgery:
❑Tuber resection
❑Multiple tuber resection
❑Temporal lobectomy
❑Other lobectomy
❑Hemispherectomy
❑Corpus callosotomy
❑Deep brain stimulation
❑Other (list)_____

Presurgical evaluation:
❑EEG
❑Video EEG
❑MRI
❑SPECT
❑WADA
❑PET-Standard
❑AMT-PET
❑ Other (list)_____

Surgical results (check all that apply):
❑No benefit
❑<50 % seizure reduction

❑50-75 % seizure reduction
❑76-90 % seizure reduction
❑91-99 % seizure reduction
❑Reduced seizure severity
❑Reduced seizure duration
❑Reduction in prior epilepsy treatment:
- ❑Polytherapy to monotherapy
- ❑AED dosage reduction
- ❑Discontinuation of AED
- ❑Removal of VNS device
- ❑Discontinuation of Ketogenic Diet

❑Seizure remission

Surgical or post-surgical complications
❑Hemorrhage
❑Hydrocephalus with shunting
❑Visual field change
❑Facial weakness
❑Motor weakness: ❑Transient ❑Persistent
❑Infection
❑Speech deficit
❑Death
❑Other (list): _____

SLEEP

Does subject have pervasive and persistent difficulties with sleep: ❑Yes ❑No ❑Unknown
If yes, what are the main difficulties (check all that apply):

Poor quality (or non-restorative) sleep:
- ❑Restless sleep
- ❑Wakes up tired
- ❑Wakes up in a bad mood
- ❑Permanently drowsy during day
- ❑Daytime naps

Anxieties about sleep:
- ❑Afraid to go to bed
- ❑Afraid of the dark
- ❑Afraid of dying during sleep
- ❑Insists on sleeping with someone else
- ❑Needs security object
- ❑Insists on bedtime rituals

Parasomnias:
- ❑Talks in sleep
- ❑Walks in sleep
- ❑Nightmares
- ❑Sleep terrors
- ❑Teeth grinding
- ❑Head banging

Disordered breathing:
- ❑Snoring
- ❑Gagging or choking
- ❑Apnoeic (cessation of breathing) episodes

Early waking:
- ❑Early morning wakening (before 0500)

Other:
- ❑Narcolepsy
- ❑Cataplexy
- ❑Other _____

❑Other _____

Has subject ever had a polysomnogram (PSG): ❑Yes ❑No ❑Unknown
If yes, what was the subject's age at most recent exam: _____ month(s) _____ year(s)
If a PSG was conducted, what were the results?
❑Unknown
❑Normal
❑Abnormal (check all that apply):

❑Obstructive sleep apnea	❑Terminal insomnia
❑Central sleep apnea	❑Findings suggestive of narcolepsy
❑Frequent arousals	❑Other _____
❑Restless legs	❑Other _____
❑Snoring	❑Other _____
❑Seizures	❑Other _____

Has subject ever received treatment for sleep disorder: ❑Yes ❑No ❑Unknown
If yes, check all that apply:

Current treatments	Previous treatments
Medications	Medications
❑Melatonin	❑Melatonin
❑Diphenhydramine	❑Diphenhydramine
❑Imipramine	❑Imipramine
❑Amitriptyline	❑Amitriptyline
❑Trazodone	❑Trazodone
❑Chloral hydrate	❑Chloral hydrate
❑Benzodiazepines	❑Benzodiazepines
❑Other _____	❑Other _____
❑Non-invasive ventilation (e.g., CPAP, BiPAP, etc.)	❑Non-invasive ventilation (e.g., CPAP, BiPAP, etc.)
_____	_____
_____	_____
❑Oral appliance for sleep disorder (e.g., Bruxism, snoring, etc.)	❑Oral appliance for sleep disorder (e.g., Bruxism, snoring, etc.)
_____	_____
_____	_____
❑Surgical intervention (e.g., adenoidectomy, tonsillectomy, deviated septum repair, etc.)	❑Surgical intervention (e.g., adenoidectomy, tonsillectomy, deviated septum repair, etc.)
_____	_____
_____	_____

OTHER NEUROLGICAL ABNORMALITIES

Were any other neurological abnormalities found: ❑Yes ❑No ❑Unknown
If yes, check all that apply:
❑Chordoma
❑ Meningioma
❑ Other (list): _____
_____

Result found by (indicate diagnostic tool): ❑ CT ❑ MRI ❑ MRA ❑ PET-standard ❑ AMT-PET ❑ SPECT
❑ Other (list): _____

Did subject have symptoms related to other abnormality: ❑Yes ❑No ❑Unknown
If yes, list: _____

Did subject have treatment for the findings indicated above: ❑Yes ❑No ❑Unknown
If yes, briefly describe: _____
_____

XII. OTHER ORGAN INVOLVEMENT

LIVER

LIVER DIAGNOSTICS

Has subject had any of the following diagnostic studies performed (choose all that apply):

- ❑US-liver/abdominal
- ❑CT-liver/abdominal
- ❑MRI
- ❑Other (list): _____

If any of the above diagnostics were performed, complete the following section. If not, skip to the Other Organs part of section XII (Other Organ Involvement).

LIVER FINDINGS

If any of the above imaging studies were performed (ultrasound, CT, MRI, angiogram, nuclear study) what were the results:

❑Unknown

	Results found by					
	CT	MRI	Angiogram	Nuclear study	Other (list)	
❑Normal	❑	❑	❑	❑	❑	❑_____
❑Abnormal:						
❑Hamartoma	❑	❑	❑	❑	❑	❑_____
❑Single lesion	❑	❑	❑	❑	❑	❑_____
❑Multiple lesions:	❑	❑	❑	❑	❑	❑_____
How many: _____ Diameter of largest lesion: _____ cm						
❑Other: _____	❑	❑	❑	❑	❑	❑_____

❑Did subject have symptoms: ❑Yes ❑No ❑Unknown

If yes, describe: _____

❑Did subject receive treatment: ❑Yes ❑No ❑Unknown

If yes, indicate treatment received: _____

OTHER ORGANS

Did subject have other organ involvement: ❑Yes ❑No ❑Unknown

If yes, check all that apply:

- ❑Thymus
- ❑Fibromatous tumors of pharynx, larynx, esophagus
- ❑Stomach tumors
- ❑Duodenum tumors
- ❑Colon/rectum polyps/tumors
- ❑Pancreas
- ❑Spleen
- ❑Gall bladder
- ❑Lymph nodes
- ❑Bone
- ❑Other _____
- ❑Other _____
- ❑Other _____

Briefly describe findings indicated above: _____

Did subject have treatment for the findings indicated above: ❑Yes ❑No ❑Unknown
If yes, briefly describe: _____
_____

XIII. GENDER SPECIFIC CONCERNS

FEMALE (if applicable)

Puberty

If subject has underage adrenarche (secondary sex characteristics), was it on time (age 6 – 8 years): ❑Yes ❑No ❑Unknown
If no, was it ❑ Early ❑ Late

If subject has undergone thelarche (breast development), was it on time (age 9-13): ❑Yes ❑No ❑Unknown
If no, was it ❑ Early ❑ Late

If subject has undergone menarche (menstruation), was it on time (age 10-15): ❑Yes ❑No ❑Unknown
If no, was it ❑ Early ❑ Late

Hormone Therapy

Has subject ever had female hormonal therapy (e.g., birth control, hormonal replacement therapy, etc.): ❑Yes ❑No ❑Unknown
If yes, is subject being currently treated: ❑Yes ❑No ❑Unknown
If yes, list any medications: _____

Pregnancy

Has subject ever been pregnant: ❑Yes ❑No ❑Unknown
If yes, number of pregnancies _____
Were there complications: ❑Yes ❑No ❑Unknown
If yes, indicate which complications occurred:
- ❑ Maternal gestational diabetes
- ❑ Maternal infection
- ❑ Maternal seizures
- ❑ Maternal substance abuse
- ❑ Premature rupture of membranes
- ❑ Premature birth
- ❑ Other (list): _____
_____

Did subject have any miscarriages or stillbirths: ❑Yes ❑No ❑Unknown
If subject delivered liveborn young, were there congenital anomalies: ❑Yes ❑No ❑Unknown
If yes, how many children were affected? _____ (list below)

	Affected child Anomalies	Mild	Moderate	Severe
Child 1	_____	❑	❑	❑
	_____	❑	❑	❑
	_____	❑	❑	❑
Child 2	_____	❑	❑	❑
	_____	❑	❑	❑
	_____	❑	❑	❑
Child 3	_____	❑	❑	❑
	_____	❑	❑	❑
	_____	❑	❑	❑
Child 4	_____	❑	❑	❑
	_____	❑	❑	❑
	_____	❑	❑	❑
	_____	❑	❑	❑

Reproductive System

Has subject had any reproductive system findings: ❑Yes ❑No ❑Unknown
If yes, check all that apply:

Type of finding	Is the finding related to TSC?		
❑Ovarian tumor	❑Yes	❑No	❑Unknown
❑Uterine tumor	❑Yes	❑No	❑Unknown
❑Other (list): _____	❑Yes	❑No	❑Unknown
❑Other (list): _____	❑Yes	❑No	❑Unknown
❑Other (list): _____	❑Yes	❑No	❑Unknown

Menopause

Has subject undergone menopause: ❑Yes ❑No ❑Unknown

If yes, was it: ❑ natural or ❑secondary to _____ Oophorectory/hysterectomy

MALE (if applicable)

Puberty

If subject has entered puberty, was it on time (age 9 - 15 years): ❑Yes ❑No ❑Unknown

If no, was it ❑ Early ❑ Late

Has subject fathered children: ❑Yes ❑No ❑Unknown

If subject delivered liveborn young, were there congenital anomalies: ❑Yes ❑No ❑Unknown

If yes, how many children were affected? _____ (list below)

Affected child Anomalies		Mild	Moderate	Severe
Child 1	_____	❑	❑	❑
	_____	❑	❑	❑
	_____	❑	❑	❑
Child 2	_____	❑	❑	❑
	_____	❑	❑	❑
	_____	❑	❑	❑
Child 3	_____	❑	❑	❑
	_____	❑	❑	❑
	_____	❑	❑	❑
Child 4	_____	❑	❑	❑
	_____	❑	❑	❑
	_____	❑	❑	❑

Reproductive System

Has subject had any reproductive system findings: ❑Yes ❑No ❑Unknown

If yes, check or list if applicable:

Type of finding	Is the finding related to TSC?		
❑Testicular tumor	❑Yes	❑No	❑Unknown
❑Other (list): _____	❑Yes	❑No	❑Unknown
_____			

XIV. OTHER MEDICAL/SURGICAL HISTORY

MEDICAL

Has subject had any significant medical conditions not related to TSC: ❑Yes ❑No ❑Unknown

If yes, list condition, and check whether condition is active:

Condition	Active		Medication	Other Treatment
_____	❑Yes	❑No	_____	_____
_____	❑Yes	❑No	_____	_____
_____	❑Yes	❑No	_____	_____
_____	❑Yes	❑No	_____	_____

_____	❑Yes	❑No	_____	_____
_____	❑Yes	❑No	_____	_____
_____	❑Yes	❑No	_____	_____
_____	❑Yes	❑No	_____	_____
_____	❑Yes	❑No	_____	_____
_____	❑Yes	❑No	_____	_____

SURGICAL

Has subject had any surgery procedure not related to TSC: ❑Yes ❑No ❑Unknown

If yes, list: _____

_____

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Appendix G – Mortality Report Tool

Tuberous Sclerosis Complex (TSC) Database
Data Collection Form -- Mortality Report

(Please print all information and check appropriate responses)

Today's Date (mm/dd/yyyy): ___/___/_____

Subject's Full Name (first/middle/last): _____

Age: _____ Date of Birth (mm/dd/yyyy):___/___/_____ Date of Death (mm/dd/yyyy):___/___/_____

Was death related to complications of TSC: ❑Y ❑N ❑U
If yes, please check category and describe (e.g. heart failure due to rhabdomyoma):

Cardiac _____
LAM _____
Renal _____
Brain lesions other than epilepsy _____
Epilepsy _____
Other _____

If cause of death was not related to TSC, please choose category and briefly describe (e.g., motor vehicle accident)
Accidental causes: _____
Other (please list):_____

Was an autopsy performed: ❑Y ❑N ❑U
If yes, where: _____ city _____ state

Is autopsy report available: ❑Y ❑N ❑U

Were any organs donated to a tissue bank (e.g., TSC Tissue Donation Program at TSA) : ❑Y ❑N ❑U
If yes, please indicate name and location of bank and physician who banked samples: _____

Comments:_____

For Center Use Only			
Database ID:	**TSC Consortium Site:**	**Medical Record #:**	
DB Consent: ❑Y ❑N	Form completed by:	Registry: ❑Y	❑N

Created on 3/9/2005 10:36 AM Date last modified: 07/14/05

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Appendix H – Aims and Hypotheses

Focused Hypotheses (November 2004 Meeting Results)

Topics:

- Variability of disease
- Inter-relationship of manifestations
- Genotype-phenotype

Specific areas of interest:

Brain
Kidney

Representative Research Questions:

Is there a predictable inter-relationship of the manifestations of TSC?

- What is the relationship between seizures, tubers and other cerebral malformations on cognitive behavioral outcome?
    - Are there regression syndromes?
    - What are the types of neuro-psychiatric problems that occur in TSC?
        - Treatments
        - ADHD
        - Learning Disability/MR
        - Autism spectrum disorder
        - Obsessive compulsive disorder
        - Depression/Bipolar disease/Anxiety
        - Sleep Disorders
    - New onset of psychiatric diagnosis in adults?

- Is there any correlation between skin manifestations and other features?
- Presence of retinal TSC lesions?
    - Yes, no, not assessed
- Seizures
    - Yes, no, age of onset, resolution of
        - Type
            - Infantile spasm
            - Generalized
            - Partial
        - Triggers
        - Severity/frequency
            - History of status epilepticus
        - Treatments
            - VNS
            - Ketogenic Diet
            - AEDs

- Surgery
  - Resective
  - Corpus Callosum
  - Deep Brain Stimulation

- Electroencephalogram
  - Type of study
  - Normal/Abnormal
    - Slowing
    - Focal discharges
    - Multifocal discharges
    - Hypsarrhytmia
    - Generalized
- Brain lesions
  - How many, where, CT vs MRI (equipment)
    - Tubers
    - Subependymal nodules
    - SEGA
    - Migration defects
- Is there a higher incidence of endocrine disease in TSC patients?
  - Diabetes
    - Weight/obesity
  - Thyroid or other endocrinopathy
  - Growth and hemihypertrophy
- If you have heart lesions could you have other vascular lesions?
  - Does the presence of rhabdomyoma put the patient at higher risk for cerebral or cerebral vascular disease?
  - Presence of arrhythmia?
    - Potential precipitators
    - Age of onset
- What is the relationship between renal AMLs, liver lesions or other abdominal lesions?
  - Presence of AMLs
  - Number of AMLs
  - Size of AMLs

Does genotype predict phenotype and offer prognostic information?

- TSC1
- TSC2
- Mutation type
- Genotype
- Modifying genes
- Sex influence
- Environmental modifiers
  - Socioeconomic status
  - Diet

Given a large enough cohort of individuals with TSC followed for a prolonged period of time, can we precisely define the range of clinical variability?

- How large is large enough?
- What are the unique problems of TSC in the adult?
  - Cardiac disease
  - Stroke
  - Dementia
  - Cause of death/age
- Duration?
- What factors of TSC are influenced by the age of the patient/s?
  - Biochemical changes/hormones
    - Puberty
    - Menstruation
    - Menopause
    - Pregnancy outcome
      - Is there a higher rate of complications for TSC moms?
      - Is there a higher rate of congenital anomalies of offspring?
    - Hormone based contraceptives of any type/HRT
    - ACTH
- How do treatment attempts affect clinical variability?
- Can we predict tumor growth?

Abbreviations:

ACTH	Adrenocorticotropic Hormone
ADHD	Attention Deficit Hyperactivity Disorder
AED	Anti-Epileptic Drug
AML	Angiomyolipoma
CT	Computed Tomography
HRT	Hormone Replacement Therapy
MRI	Magnetic Resonance Imaging
MR	Mental Retardation
TSC	Tuberous Sclerosis Complex
VNS	Vagus Nerve Stimulator

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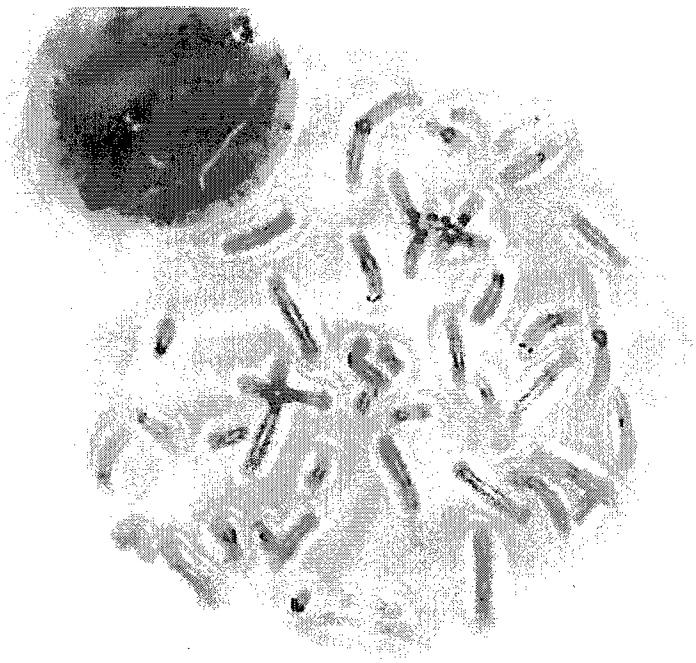
Appendix I – TSC/LAM International Research Symposium program/abstract

Tuberous Sclerosis Alliance

TSC/LAM International Research Symposium



April 8-10, 2005 • Cincinnati, Ohio

Sponsored by . . .

National Institute of Neurological Disorders and Stroke

Office of Rare Diseases

National Institutes of Health

Clinical Features and Natural History of TSC

Steven P Sparagana and E. S. Roach
Department of Neurology, Texas Scottish Rite Hospital for Children and the University of Texas Southwestern Medical Center (Dr. Sparagana) and the Department of Neurology and Comprehensive Epilepsy Center, Wake Forest University School of Medicine, Winston-Salem, NC (Dr. Roach)

We will use the consensus diagnostic criteria for tuberous sclerosis complex (TSC) as the framework to review many of the common clinical features of TSC and their natural history. The major cutaneous findings of TSC include facial angiofibromas, ungual fibromas, hypomelanotic macules (which occur in over 90% of the individuals with TSC), and the shagreen patch. Retinal hamartomas occur in up to 75% of individuals with TSC but; these are sometimes useful in establishing the diagnosis but do not typically cause clinically significant deterioration of vision. Cardiac rhabdomyomas occur in about two thirds of neonates with TSC and can be lethal in babies whose cardiac output is compromised; after the neonatal period, however, rhabdomyomas tend to shrink and do not typically become symptomatic aside from the occasional older person who develops a cardiac arrhythmia. Renal angiomyolipomas (AMLs) are present in about 75% of individuals with TSC by age 10 years but seldom cause symptoms before adolescence or adulthood. These renal tumors typically enlarge very slowly, and it is unusual for an AML to cause symptoms before adulthood, although renal AMLs are said to be the most common cause of death among adults.

Over 90% of the TSC patients in some series have epileptic seizures, although these do not always continue indefinitely and the seizures are not always intractable to medical or surgical management. Some individuals with epilepsy due to TSC are even able to successfully discontinue antiepileptic medication. The frequency of mental retardation has clearly been overestimated in previous years. Some estimates suggest that about half of the individuals with TSC have significant cognitive impairment, although some people without mental retardation will nevertheless have significant behavioral issues that are attributable to TSC. Giant cell astrocytomas occur in about 10% of the patients with TSC. Almost all of the giant cell tumors occur in children and are located near the anterior horn of the lateral ventricles. If detected early, giant cell tumors can be surgically removed with good results.

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Appendix J – Curriculum Vitae Jo Anne Nakagawa

JO ANNE NAKAGAWA
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Valencia, CA 91355-3025
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joannenakagawa@aol.com

CAREER OBJECTIVE

To seek a challenging management or research position in health care or biopharmaceutical industry where I can utilize my exceptional clinical/technical knowledge and organizational skills in clinical trial coordination/management, medical research, and my excellent interpersonal skills with the study team, research subjects and their families.

EDUCATION

University of California, Los Angeles – B.A., Biology 1970 to 1975
The American Registry of Diagnostic Medical Sonographers (Current Status - Inactive) 1983 to 1989

EXPERIENCE

SENIOR PUBLIC ADMINISTRATION ANALYST 1989 to Present
UCLA DIVISION OF PEDIATRIC NEUROLOGY, LOS ANGELES, CA

- Extensive experience in regulatory management and coordination of pediatric epilepsy trials.
  - Assess protocol feasibility, prepare and submit regulatory and budget documents
  - Recruitment and subject screening; case report form completion, drug accountability, laboratory and adverse events monitoring, and write study visit summaries.
- Experience in regulatory management of other pediatric research, including autism, congenital myasthenia, and genetics of epilepsy.
- Manage physician investigational new drug (IND) studies.
  - Prepare annual and routine regulatory submissions to the UCLA Medical IRB and the FDA.
  - Co-monitored nine investigational sites participating in a multi-center, randomized infant epilepsy trial with a total enrollment of 228 subjects.
  - Co-authored interim study report of safety and efficacy results, which was submitted to the FDA.
- 25% time (from 2004 to present) spent in research laboratory performing acute studies in immature rats given varying duration of status epilepticus to determine the frequency and severity of spontaneous seizures and assessment of neuronal injury by histological methods.

STAFF RESEARCH ASSOCIATE 1981 to 1989
UCLA DIVISION OF PEDIATRIC NEUROLOGY LOS ANGELES, CA

- Provide technical assistance for the UCLA Pediatric Epilepsy Program
  - Performed neonatal electroencephalograms under supervision of a registered pediatric EEG technologist.
  - Transferred EEG recordings on paper using standard EEG montages and correlate behavioral events captured on video recordings.
- Completed a didactic sonography course in Los Angeles and passed the American Registry of Diagnostic Medical Sonagraphy (RDMS) exam after two years of on-the-job experience doing daily intracranial ultrasounds on premature infants enrolled in a NIH-funded research study.
- Performed intracranial ultrasounds in the UCLA neonatal intensive care and observation units for clinical indications (i.e. not research).
- Performed creatine phosphokinase assay in the research lab for a study of intracranial hemorrhage in premature infants.

STAFF RESEARCH ASSOCIATE 1980 to 1981
UCLA DIVISIONS OF NEONATOLOGY AND PEDIATRIC NEUROLOGY, LOS ANGELES, CA

- Experience in tissue culturing & thin layer chromatography, and provided technical support for research studies on the effect of antiepileptic drugs on the developing (rodent) brain.

STAFF RESEARCH ASSOCIATE 1976 to 1979

UCLA DEPARTMENT OF PEDIATRICS, DIVISION OF NEONATOLOGY , LOS ANGELES, CA

- Provided technical support for research of retinopathy of prematurity in an animal model and other α-tocopherol (Vitamin E) research studies.
- Assisted principal investigator with lung maturation research studies doing light and electron microscopy of lung tissue from newborn animal model.

LABORATORY ASSISTANT 1975 to 1976

UCLA Department of Medicine; Rheumatology Division, Los Angeles, CA

- Assisted senior staff research associate with rheumatoid arthritis studies using radioisotope-labeled (Iodine-131) human leukocytes.
    - Experience with preparation of human blood, and use of microscope, and gamma-counter.

MANUSCRIPTS

Rintahaka P, **Nakagawa J**, Shewmon DA, Kyyronen P, Shields WD. Incidence of death in patients with intractable epilepsy during nitrazepam treatment. Epilepsia April 1999, Volume 40 (4), 492-496.

Shields WD, Shewmon DA, Peacock WJ, LoPresti C, **Nakagawa J**, Yudovin S. Surgery for the treatment of medically intractable infantile spasms: A cautionary case. Epilepsia 40 (9): 1305-1308, 1999.

Elterman RD, Shields WD, Mansfield KA, **Nakagawa J.** Randomized trial of vigabatrin in patients with infantile spasms. Neurology 57:1416-1421, 2001.

EXTRACURRICULAR ACTIVITIES

MEMBERSHIP

Association of Clinical Research Professionals
Epilepsy Foundation of America
American Epilepsy Society

NON-PROFIT ORGANIZATIONS

Help the Afghan Children (HTAC) – Wrote and illustrated two children's storybooks in 2003 ("Ahmad's Kite" and "A New School in the Village: Leyla's Gift"), which are bilingual in English and Dari. 8000 copies were distributed to primary schools in Afghanistan built by HTAC. Wrote and illustrated a third storybook ("The Storyteller") in Fall 2004 with a planned distribution in 2005.

Tuberous Sclerosis Alliance (TSA) – July 2004 to February 2005: Active participant of the Speaker's Planning Committee for the Western Regional Conference held in Riverside, CA February 19-20, 2005.

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Appendix K – Curriculum Vitae of Michael Cinkosky

Michael Cinkosky

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Denver, Colorado 80209
michael@cinkosky.com
720-323-9440

Professional Positions

President; Third Street Software, Inc., Denver, Colorado; 2003-Present.

Vice President, Software Development; Transgenomic, Inc., Denver, Colorado; 2001-Present.

Director, Product Management; Genomica Corp., Boulder, Colorado; 2000-2001.

Director, Informatics; Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah; 1995-2000.

Director, Information Systems, and member of the Board of Directors; National Center for Genome Resources, Santa Fe, New Mexico; 1994-1995.

Scientific Staff Member; Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, New Mexico; 1989-1994.

Consultant; Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, New Mexico; 1984-1989.

President; Cimarron Data Systems, Inc., Santa Fe, New Mexico; 1984-1989.

Grants and Contracts

Investigator, "Rocky Mountain Cancer Genetics Network," NIH,1999-2000.

Investigator, "Familial Colon Cancer Clinic," NIH 1998-2000.

Director, Informatics Core, "Cancer Center Support Grant," NIH, 1997-2000.

Investigator, "High Risk Breast Cancer Clinic," NIH, 1996-2000.

Principal Investigator, "The Genome Sequence Data Base," DOE/OHER 1993-1995.

Principal Investigator, "SIGMA: System for Integrated Genome Map Assembly," DOE/ OHER 1992-1994.

Co-Principal Investigator, "GenBank," NIH Contract #1-GM-7-2110, 1992-1993.

Co-Principal Investigator, "GenBank at Los Alamos," NLM Agreement #1Y01-LM-10011, 1991-1993.

Education

B.A., St. John's College, Arts and Sciences, Santa Fe, NM, 1984.

Selected Software Systems

Sente™, a biomedical literature research application (2004)

WAVE Navigator™, DHPLC instrument control software (2002-2004)

www.MutationDiscovery.com, a web-based genetic research system (2002-2004)

Utah Population Database, (1995-2000)

DNA Sequencing Core Facility LIMS (2000)

Rocky Mountain Cancer Genetics Network Participant Tracking System (2000)

Requisition and Purchase Tracking System (1999)

Bone Marrow Transplant Patient Tracking System (1998)

Microarray Core Facility LIMS (1998)

Familial Colon Cancer Subject Registry (1997)

High Risk Breast Cancer Clinic Patient Tracking System (1996)

SIGMA, System for Integrated Genome Map Assembly (1992-1994)

GenBank (1987-1992)

The Selling Point™, a retail management application (1984-1989)

Selected Publications

Cinkosky, M.J., Fickett, J.W., and Keen, G.M., A New Design for the Genome Sequence Data Base, *IEEE Engineering in Medicine and Biology* **14**:725-729 (1995).

Waterman, M., Uberbacher, E., Spengler, S., Smith, F.R., Slezak, T., Robbins, R.J., Marr, T., Kingsbury, D.T., Gilna, P., Fields, C., Fasman, K., Davison, D., Cinkosky, M., Cartwright, P., Branscomb, E., Berman, H.,

Report of the Invitational DOE Workshop on Genome Informatics, 26-27 April 1993, Baltimore, Maryland; Genome Informatics I: Community Databases, Robbins, R., Ed., *Journal of Computational Biology* **1,** 173 -190 (1994).

Fickett, J.W. and Cinkosky, M.J., A Genetic Algorithm for Assembling Chromosome Physical Maps, *Proceedings of the Second International Conference on Bioinformatics, Supercomputing, and Complex Genome Analysis,* Lim, H.A., Fickett, J.W., Cantor, C.R., and Robbins, R.J., Eds., World Scientific, (1993).

Mandel, JL, Monaco, AP, Nelson, DL, Schlessinger, D, Willard, HF, Chipperfield, M, Pearson, P, Gilna, P and Cinkosky, M; Genome maps III. 1992. Wall Chart. *Science* **258**:5079, 87-102 (1992).

Stallings, R.L., Doggett, N.A., Callen, D., Apostolou, S., Chen, L.Z., Nancarrow, J.K., Whitmore, S.A., Harris, P., Michison, H., Breuning M., Saris, J.J., Fickett, J., Cinkosky, M., Torney, D.C., Hildebrand, C.E., and Moyzis, R.K., Evaluation of a Cosmid Contig Physical Map of Human Chromosome 16, *Genomics* **13,** 1031-1039 (1992).

Keen, G.M., Lawton, J.R., Cinkosky, M.J., Fickett, J.W., Mishra, S.K., Burks, C., Access to Molecular Biology Databases, *Mathematical and Computer Modeling,* **16,** 93-101 (1992).

Cinkosky, M.J., Fickett, J.W., Gilna, P., and Burks, C., Electronic Data Publishing and GenBank, *Science* **252,** 1273-1277 (1991).

Burks, C., Cassidy, M., Cinkosky, M.J., Cumella, K.E., Gilna, P., Hayden, J.E.-D., Keen, G.M., Kelley, T.A., Kristofferson, D., and Ryals, J., GenBank, *Nucleic Acids Research*, **19,** 2221-2225 (1991).

Cinkosky, M.J., with others, The Human Genome Information Resource, *DOE Human Genome Report,* Mansfield, E., Ed., Oakridge National Laboratory, Oakridge, TN (1990).

Cinkosky, M.J., with others, GenBank: Current Status and Future Directions. *Methods in Enzymology* **183,** 1-22 (1989).

Cinkosky, M.J., Nelson, D., Marr, T.G., A Technical Overview of the GenBank/HGIR Database, Los Alamos Unclassified Report #88-3038 (1988).

Atencio, E.J., Bilofsky, H.S., Burks, C., Bossinger, J., Cinkosky, M.J., Esekogwu, V.I., Fickett, J.W., Foeller, C., Foley, B.T., Goad, W.B., Hayden, J.E.-D., Lewitter, F.I., Lopez, N., MacInnes, K.A., Marr, T.G., Martinez, A.V., Martinez, F.A., McLeod, M.J., Mishra, S.K., Nelson, D., Rindone, W.P., Schermer, C.R., Smith, M.T., Swindell, C.D., Trujillo, B.L., and Tung, C.-S. The GenBank Genetic Sequence Data Bank. *Nucl. Acids Res.,* **16:**1861 -1863 (1988).

Cinkosky, M.J., Fickett, J., Nelson, D., The Restructuring of GenBank, Los Alamos Unclassified Report #88 -1255 (1987).

Atencio, E.J., Bilofsky, H.S., Bossinger, J., Burks, C., Cameron, G.N., Cinkosky, M.J., England, C.E., Esekogwu, V.I., Fickett, J.W., Foley, B.T., Goad, W.B., Hamm, G.H., Hazledine, D.J., Kahn, P., Kay, L., Lewitter, F.I., Lopez, N., MacInnes, K.A., McLeod, M.J., Melone, D.L., Myers, G., Nelson, D., Nial, J.L., Norman, J.K., Rasmussen, E.D., Revels, A.A., Rindon, W.P., Schermer, C.R., Smith, M.T., Stoesser, G., Swindell, C.D., Trujillo, B.L., and Tung, C.-S. *Nucleotide Sequences 1986/1987: A Compilation from the GenBank and EMBL Data Libraries.* Academic Press, Orlando, FL (1987).

Fickett, J.W., Cinkosky, M.J., Burks, C., Goad, W.B., Mishra, S.K., and Tung, C.-S. Management of the Data Associated with Large-Scale Sequencing and Mapping. *Biophys. J.,* **51,** 440a (1987).

Armstrong, J., Atencio, E.J., Bergman, B.E., Bilofsky, H.S., Brown, L.B., Burks, C., Cameron, G.N., Cinkosky, M.J., Elbe, U., England, C.E., Fickett, J.W., Foley, B.T., Goad, W.B., Hamm, G.H., Hayter, J.A., Hazledine, D., Kanehisa, M., Kay, L., Lennon, G.G., Lewitter, F.I., Linder, C.R., Luetzenkirchen, A., McCaldon, P., McLeod, M.J., Melone, D.L., Myers, G., Nelson, D., Nial, J.L., Perry, H.M., Rindone, W.P., Sher, L.D., Smith, M.T., Stoesser, G., Swindell, C.D., and Tung, C.-S. *Nucleotide Sequences 1985: A Compilation from the GenBank and EMBL Data Libraries.* IRL Press, Oxford, UK (published as four volumes: Parts I-IV) (1985).

Other Activities

Grant reviewer for National Institutes of Health, National Science Foundation, and the U.S. Department of Energy.

October 2004

Appendix L – Letter from Tuberous Sclerosis Alliance (Nancy Taylor)

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Silver Spring, MD 20910

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Phone: (301) 562-9890
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E-mail: info@tsalliance.org

September 21, 2005

Dear Friends:

I'm writing to update you with some exciting news about the Tuberous Sclerosis Complex (TSC) Clinical Database project. I'm pleased to announce that the project is continuing its forward momentum with the TS Alliance assuming responsibility to develop and maintain the database. On behalf of the TS Alliance Board of Directors and the TSC Clinics across the country, I want to thank Texas Scottish Rite Hospital for Children for coordinating initial efforts on the database project. I also want to acknowledge the input from all members of the TSC Clinical Database Consortium. The initial work on the database has proven to be invaluable.

"We at Texas Scottish Rite Hospital for Children are grateful and honored to have played a significant role in the establishment of the Tuberous Sclerosis Complex Clinical Consortium and in the initial efforts to create a Tuberous Sclerosis Complex (TSC) Clinical Database. The collaboration between members of the TSC clinical research community and the TS Alliance has been fruitful," said Steven P. Sparagana, M.D., TSC Clinic Director at Texas Scottish Rite Hospital for Children and Principal Investigator of the DOD-funded TSC Natural History Study Development Award. "We applaud the TS Alliance's initiative to house the database, and we are ready and willing to transfer the task of database development and construction back to them. Our intent is to continue working with the TS Alliance and the Consortium to make the database a reality. These efforts will help all of us not only understand the nature of TSC better, but will also ultimately serve the fundamental purpose of helping to improve the lives of those affected by TSC."

Briefly, the TSC Clinical Database Project will allow the TS Alliance to enable and support research based on a vast array of data stored in a comprehensive information repository. All TSC Clinics will be invited to participate in collecting information that will provide valuable data on how TSC affects individuals throughout their lifespan – from birth to death. The database will incorporate the full range of TSC clinical information, combine data collected from multiple sources and, for the first time, make that information available to researchers. To be successful, the project will require collecting information from large numbers of individuals with TSC, including the complete range of symptoms (the phenotype) along with associated genetic (genotype) and demographic data.

The TS Alliance has contracted with Michael Cinkosky of Tesuji, Inc., to create the database. Michael has been leading teams that design and build software for biomedical laboratory and clinical research for more than 20 years. His team at Tesuji, Inc. has worked together on various projects ranging from commercial software applications to custom databases for both not-for-profit and commercial organizations.

Jo Anne Nakagawa will facilitate the project internally for the TS Alliance. She joined our staff as Director of Clinical Projects in August after working at UCLA in basic and clinical research for more 30 years. She has more than 15 years experience in clinical trials coordination in the Division of Pediatric Neurology. Her experience includes managing several physician-initiated investigational new drug (IND) studies such as the only U.S. multi-center vigabatrin study for patients with infantile spasms, which was conducted from 1996 to 2001. Jo Anne also will serve as our organization's liaison to the TSC Clinics; collaborate with TSC researchers, advisors, board members and staff; facilitate data sharing; and develop outreach programs to engage clinical science researchers to advance identifying treatments and the cure for TSC.

I will keep you informed as the project develops. In the meantime, if you have any questions, please free to contact me via email at ntaylor@tsalliance.org or call me at (800) 225-6872.

Regards,

Nancy Taylor

Nancy L. Taylor, CEO

Appendix M – Tesuji, Inc. Development Plan

Tuberous Sclerosis Alliance
TSC Clinical Database

Project Definition

This Project Definition describes the scope, goals, and expectations for the Tuberous Sclerosis Complex (TSC) Clinical Database project for the Tuberous Sclerosis Alliance (TSA).

Motivation

This project will construct a central research repository for detailed information about patients with Tuberous Sclerosis Complex (TSC), a debilitating condition that affects some 50,000 Americans and perhaps one million people worldwide.

At present, a central information resource about TSC patients does not exist. Researchers who study the condition must attempt to obtain patient records from individual hospitals and clinics, or use their own records. In either case, gathering consistent and comprehensive information about more than a handful of patients is difficult or impossible for many involved in research in this area. This lack of a comprehensive information resource is limiting the types and scale of research projects that can be undertaken in this field.

To be successful, these research efforts require specific information about large numbers of patients. These data include the complete range of symptoms (phenotypes) along with associated genotype and demographic data. Studying these patterns along with patient histories and their responses to various diagnosis and treatment methods would enable researchers to improve clinical care. This will also help us gain a much better understanding of the disease mechanisms – essential to someday finding a cure.

The TSC Clinical Database Project will allow the Tuberous Sclerosis Alliance (TSA) to enable and support this kind of much needed research. By having a system that can handle the full range of TSC patient data, the TSA will be prepared to collect and combine patient data from multiple sources and, for the first time, make that critical information available in a useful form to researchers.

Scope

For this project we will develop the following components:

Database

The database will store information on TSC patients. In addition to general demographic information, the database will include detailed information some or all of the following areas:

- Neurology
- Dermatology
- Cardiology
- Behavior, Cognition, and Psychiatry
- Epilepsy and EEG
- Genetics
- Renal
- Imaging
- Medical History and Family History
- OB/GYN/Reproductive Issues

The final selection of areas of focus, and the exact content of the database in each of these areas, will be determined in collaboration with the TSA staff and working groups organized by the TSA and including physicians and researchers working in each area.

This will be a password-protected, relational database, maintained on a secure server.

Data Entry and Editing Interface

An easy-to-use, cross-platform, web-based interface will allow for secure data entry and editing by TSA staff. These users will be able to access this

interface from anywhere with an Internet connection, enabling them to work in most clinical environments. All communication of data using this interface will be encrypted, preventing unauthorized access.

This interface will be available to TSA staff only.

Data Reporting and Exporting Interface

The system will include a basic data reporting interface that will enable TSA staff to easily generate summary statistics about the contents of the database, and to export data subsets for use in research projects.

Administration Tools

The system will include an interface for routine administrative tasks such as user account creation, account removal, and access privilege adjustments. There will also be an automated backup system for routinely producing archive copies of the database.

Exclusions

For clarity, we list here several areas of functionality that will not be considered within the scope of this project.

No Data Analysis Tools

The system will not include data analysis features. Instead, people who desire to perform analysis on data in this system will make use of export files that can be read by various data analysis tools.

No Data Entry

This project covers only the design and creation of the database and supporting software, not the population of the database. This work will be performed by TSA staff, or other people acting on behalf of the TSA.

No Automated Data Entry Tools

The system will not include any automated data entry tools for directly importing data from other systems. This means, for example, that data from individual medical records will need to be entered into this system manually, even if that data appears in an electronic medical record.

No Development of Questionnaire

The TSA may choose to use a questionnaire to collect data in hardcopy form, rather than entering data directly on-line. Design and production of such a questionnaire is outside the scope of this project.

Intended Users

The system is intended to be used by several different types of users. It is important that each of these groups be represented during the analysis and design of the system.

TSA Data Collection and Curation Staff

At the discretion of TSA, certain staff members will be granted access to the system in order to enter collected patient data, generate reports, and share data with researchers.

TSA Management

Some TSA managers may use the system only for generating data summary reports and for tracking the data collection process.

TSA System Administrator

At least one person must act as a system administrator to perform maintenance functions such as setting up user accounts and assigning user access privileges.

Other Affected Individuals

There are other groups of people who, while not direct users of the system, will be affected by its development and therefore should have influence on its development. This includes:

TSC Patients

Given that the purpose of the system is to track detailed medical information about TSC patients, they obviously represent an essential constituency that must be represented during the analysis and design process.

The TSC Research Community

This system will be designed to support the researchers who will use the data it contains. Researchers must be consulted to be sure that their needs are addressed in the analysis and design. This includes both the scope of the data to be collected, and the form in which it will be distributed to approved research projects.

General Requirements

There are several high-level requirements that the system must satisfy.

The system must be extensible

The system must be easily extended to accommodate new data types should they become needed at any time in the future.

The system must be secure

Access to the system must be password-controlled, and all data communication must be encrypted to prevent unauthorized access. The system must support several levels of access permission so that users can be granted access only to the functionality and data that they require to perform their jobs.

The user interface must be platform-neutral

The user interface must be platform-neutral, such that its use will not require a particular web browser or operating system.

Use of web-related communications protocols.

The user interface shall rely only on standard web-related communication protocols (e.g., http, https) to reduce the possibility that its use would conflict with firewalls or other security measures in place in clinics.

Assumptions

We are making the following assumptions, all of which are important for the success of this project:

The TSA will assemble a steering committee.

In order to make effective decisions quickly throughout the course of this project, it is essential that there be a relatively small group of people (e.g., 5 - 10) who have the authority to make decisions about the design and development of this project. We are assuming that the TSA will assemble this group at the beginning of the project and that it will remain intact throughout the entire project. This group will be required to review documents, meet occasionally (either in person, or by telephone), and represent all of the intended users and other people who will be affected by this project.

TSA staff will be available to answer questions.

TSA staff will be available as critical information resources for Tesuji for the duration of the project. This includes availability for occasional in-person interviews, telephone conversations or conference calls, and timely email exchanges.

TSA staff will facilitate communication between Tesuji and the working groups.

Efficient communication with the working groups to obtain information and approval of documentation and designs will be essential to the timely completion of this project. Tesuji will depend on TSA staff to facilitate this interaction.

All prior working group documentation will be available.

We will need all current, relevant documentation from the various working groups so that we do not need to begin from scratch on the analysis process — something that would certainly frustrate at least some members of these working groups.

TSA will obtain whatever regulatory and legal approvals are required for the implementation and operation of the system.

The operation of a database system that will contain medical records may be subject to certain regulatory restrictions. It is the responsibility of the TSA and their counsel to ensure that any required Institutional Review Board approval is obtained and that any special regulatory requirements are communicated to Tesuji as early as possible in the design process.

Technology selection

The system will be constructed using the following technology:

- Java Server Pages (JSPs),
- the open-source MySQL database, and
- the WebObjects development environment and application server.

There are no licensing fees for any of these components.

Tesuji will provide system hosting.

Although the system will be designed to be hosted anywhere, we will proceed under the assumption that, for simplicity and ease-of-support, Tesuji will provide hosting services at the time of deployment

and provide ongoing hosting services for a negotiated fee.

Constraints

No constraints have been identified at this time.

Deliverables

During this project we will deliver:

System Design Documentation

Tesuji will deliver to the TSA the following system design documentation:

- At the end of the Analysis Phase, the documentation will include a detailed domain model, including all information to be tracked by the final system, and workflow models showing how the system will be used.
- At the end of the Design Phase, the documentation will include: the database schema and annotated images of all important user interface screens.

The contents of all of the system design documentation will be subject to TSA approval.

The Deployed System

We will provide a deployed, installed, configured, and fully running system that meets the specifications in the System Design Document.

User Guide

A concise, easy-to-follow user guide will be provided for system users.

Training

We will provide up to two full days of user training at any site of TSA's choosing near the time of the delivery of the final system.

Source File Archive

All source code, libraries, installation tools, and instructions will be provided electronically so that the TSA will have everything it needs to modify and/or redeploy the system if it chooses to do so at some future date. Although we would hope to be involved in any future development, we believe TSA should have all options available.

Risks

It's important to keep in mind the risks associated with any endeavor — this helps identify and resolve problems early, so that the project can be completed as quickly and as efficiently as possible.

Access to Required Information

Access to people and information needs to be timely, efficient, and, when decisions need to be made, definitive. Poor access/availability can slow down development and delay completion.

Community Acceptance

Ultimately the success of this project depends on researchers getting the information they need to help the people with Tuberous Sclerosis Complex. This means the research community must be "on board" with this endeavor both during development (to ensure we are giving them what they need) and after deployment (to ensure they actually use it). Community acceptance must be a fundamental driving force guiding every aspect of development.

Regulatory Approval

If the TSA is required to obtain, for example, Institutional Review Board approval for this project, there is a risk that this approval will not be obtained. Lack of any required approval would jeopardize the entire project.

TSC Patient and Family Acceptance

Medical data can only be collected on patients who freely consent. Anything that limits the rate of patient consent would have a negative effect on the overall success of this project.